IDIOPATHIC INTRACRANIAL HYPERTENSION

by

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ABSTRACT

Idiopathic intracranial hypertension (IIH) is common in obese women and can lead to significant visual impairment. The cause of IIH is unknown and management controversial, due to the lack of prospective trials. This thesis provides a comprehensive review of the aetiology and management of IIH. The hypothesis that IIH is associated with a pro-inflammatory cytokine profile, suggested by its established association with female gender and obesity, was tested. Laboratory studies demonstrated the novel finding of elevated leptin in the cerebrospinal fluid from women with IIH, suggesting a role in the pathogenesis of IIH. The first randomised controlled trial in IIH is then reported. Treatment with acetazolamide was examined prospectively in 50 patients, providing seminal information to guide the design of future large-scale trials and data on the natural history of the condition. The observation that management of IIH is guided by a variety of clinical parameters was translated into a simple composite scoring system which was prospectively tested. Visual fields and optic disc appearance are shown to have the greatest influence on clinical outcome. Finally, a systematic study of the evaluation of papilloedema in IIH highlights the major limitations of the widely adopted Frisen staging scheme in the condition.

DEDICATION

For my mother,

Evelyn Jean Ball

1937-2008

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BMI	Body mass index
CSF	Cerebrospinal fluid
CTV	Computed tomogram venography
CVST	Cerebral venous sinus thrombosis
ELISA	Enzyme linked immunosorbent assay
HADS	Hospital Anxiety and Depression Score
HGF	Hepatocyte growth factor
ICP	Intracranial pressure
IIH	Idiopathic intracranial hypertension
IL	Interleukin
LogMAR	Logarithm of minimum angle of resolution
MCP	Monocyte chemoattractant protein
MD	Mean deviation
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography
NGF	Nerve growth factor
NPY	Neuropeptide Y
OCT	Optical coherence tomography
PAI	Plasminogen activator inhibitor
SF-36	Short Form 36
TNF	Tumour necrosis factor

CHAPTER 1 INTRODUCTION

1.1 Clinical Characteristics

1.1.1 Historical Background

Idiopathic intracranial hypertension (IIH) is the most recent of a number of names for the clinical syndrome of elevated intracranial pressure, without enlargement of the cerebral ventricles and in the absence of space occupying lesions. The German physician Heinrich Quincke (1983) published what is widely regarded as the first description of the condition, calling it 'meningitis serosa'. This appeared to be preceded by case reports describing the same condition as early as 1866. (Johnston et al., 2007) A second German neurologist, Max Nonne, (1904) identified cases of apparent cerebral tumour whose subsequent clinical course appeared to preclude a diagnosis of tumour, coining the term 'pseudotumour cerebri'. From 1931 onwards, An English neurologist, Sir Charles Symonds, wrote a series of papers describing children who had elevated intracranial pressure in association with middle ear disease, which he called 'otitic hydrocephalus', suggesting that the raised pressure was a result of excess cerebrospinal fluid (CSF). (Symonds, 1956)

By the turn of the 20th century, the terms serous meningitis and pseudotumour cerebri had been adopted, but diagnosis relied on clinical features or post mortem findings. Cerebral pneumography permitted further study of the condition in live patients and this was later to be enhanced by ventriculography and encephalography. Around this time Davidoff and Dyke (1956) published a report of 15 cases with normal cerebral pneumography, all of whom improved with cranial decompression. In 1937, the American neurosurgeon Walter Dandy

(1937) described 22 cases of 'intracranial pressure without brain tumour' and is credited with the first diagnostic criteria for the condition.

Foley (1955) published a detailed study dividing cases of the condition into those associated with ear disease and those with no known cause of raised intracranial pressure. He regarded hydrocephalus as an inappropriate term, since the cerebral ventricles were not enlarged and introduced the name 'benign intracranial hypertension' for non-otitic cases. He described amongst this cohort of predominantly female, young, overweight patients "a variety of proposed aetiological agents so numerous and diverse that one must suspect that none is a direct cause." The term benign intracranial hypertension was used for many years until several reports of severe visual loss in the condition rendered the term 'benign' inappropriate.

1.1.2 Definition

With the advent of complex neuro-radiology, it has been possible to identify intracranial lesions and vascular pathologies in patients who might previously have been labelled as having IIH by one of its many names. Older reports were likely to have included patients in whom cerebral venous sinus thrombosis (CVST) had not been excluded since imaging techniques were in their infancy. The clinical presentation of CVST is identical to that of IIH, but the outcome and management is dramatically different and CVST carries a significantly worse prognosis. It is essential that CVST is excluded before a diagnosis of IIH is made.

The diagnostic criteria have undergone several modifications over the years. Strict criteria now exist to ensure that a diagnosis of IIH is only applied to patients in whom all other

causes of intracranial hypertension have been excluded. (Friedman and Jacobson, 2002) These are shown in table 1.1 and are often referred to as 'modified Dandy criteria'.

Table 1.1 Diagnostic Criteria of Idiopathic Intracranial Hypertension (Friedman and Jacobson, 2002)

- If symptoms and / or signs are present, they may only reflect those of generalised intracranial hypertension or papilloedema
- Intracranial pressure, as measured in the lateral decubitus position, is elevated
- The composition of the cerebrospinal fluid is normal
- There is no evidence of hydrocephalus, mass, structural or vascular lesion
- No other cause of intracranial hypertension has been identified.

Despite widely accepted criteria, controversy still surrounds the definition of IIH as a discrete clinical entity. Pseudotumour cerebri syndrome is still used by many to describe patients with the condition, as an 'umbrella' term that can include those cases where a causative factor is strongly suspected. (Johnston et al., 2007) Confusion arises as a result of the alleged association of the condition with various medical conditions and treatments, most of which have only been described in case reports or small series. Some researchers argue for the criteria to be relaxed, so the syndrome can include focal CNS abnormalities, radiological abnormalities relating to cerebral venous outflow obstruction and CSF abnormalities. (Johnston et al., 2002) In such cases, the term 'pseudotumour cerebri syndrome' may have a place. However, where there is convincing evidence that a drug or disease is causally or temporally related, the term secondary intracranial hypertension is more appropriate.

1.1.3 Epidemiology

1.1.3.1 Incidence

Early attempts to measure the incidence of IIH, or the syndrome by one of its alternative names, are likely to have overestimated the number of cases, due to the inclusion of intracranial hypertension secondary to venous sinus thromboses or other conditions difficult to elicit by older investigative techniques. In addition, most of the largest studies of incidence to date were completed prior to the widespread acceptance of the modern diagnostic criteria (Friedman and Jacobson, 2002), so the actual incidence of 'truly idiopathic' IIH is by no means certain.

Around the world, a small number of population studies have attempted to measure the overall incidence (table 3.2). In the USA, Durcan et al (1988) reported the one-year incidence in the general population of Iowa to be 0.9 per 100,000 and of Louisiana, 1.07 per 100,000. A prospective longitudinal study in the well-defined population of Benghazi, Libya generated an annual incidence rate of 2.2 per 100,000.(Radhakrishnan et al., 1993) In Hokkaido, Japan, only two cases were found from the study of a population of around 5.8 million, giving a crude rate of 0.03 per 100,000.(Yabe et al., 2000). A review of all cases diagnosed in Belfast, Northern Ireland between 1991 and 1995 led to an overall incidence of 0.6 per 100,000.(Craig et al., 2001) Researchers in Israel reported an incidence of 0.57 to 0.94 per 100,000 general population, through the identification of 91 new cases during a one-year study period amongst a population counted by census of 5,970,000.(Kesler and Gadoth, 2001).

Table 1.2: Published studies of IIH Incidence

Year	*Location*	*Author*	*Population size*	*IIH Incidence per 100,000*
1988	Iowa, USA	Durcan et al (1988)	2,913,808	0.9
1988	Louisiana, USA	Durcan et al (1988)	4,480,681	1.07
1993	Benghazi, Libya	Radhakrishnan et al (1993)	519,000	2.2
2000	Hokkaido, Japan	Yabe et al (2000)	5,780,000	0.03
2001	Belfast, N Ireland	Craig et al (2001)	1,640,000	0.6
2001	Israel	Kesler & Gadoth (2001)	5,970,000	0.75

Incidence studies in IIH used a variety of ascertainment methods to study populations with different ethnic and genetic mixes. Taking all of these figures together and accepting the limitations of the data, an incidence of 1 in 100,000 people would seem a reasonable approximation. Thus in the general population, IIH is a relatively uncommon condition, similar in incidence to pituatory tumours, Guillain Barré Syndrome (acute inflammatory polyneuropathy) or cluster headache. However, confining studies to women aged 20-44 years, who are 20% or more above their ideal body weight, increases the incidence to 15-19 cases per 100,000,(Durcan et al., 1988) approaching that of more common conditions such as motor neurone disease and multiple sclerosis. The condition is certainly encountered by most UK neurology and ophthalmology centres on a regular basis. With the escalating prevalence of overweight and obesity around the world, it seems likely that the incidence of IIH will also increase.

1.1.3.2 Gender and age distribution

There is no doubt that IIH is more common in women. Reported female to male ratios from larger studies include 4.3:1,(Durcan et al., 1988), 5.7:1 (Craig et al., 2001), 8:1,(Kesler et al., 2000) 9.3:1, (Galvin and Van Stavern, 2004), 11.5:1(Mezaal and Saadah, 2005) and 15:1.

(Radhakrishnan et al., 1993) Some differences in clinical features between male and female patients have been described, as discussed later in the chapter.

IIH is predominantly a disease of younger adults. In one major study, 59% of patients were in the third decade of life at diagnosis,(Durcan et al., 1988) and mean ages at onset of symptoms have been reported by others as 28,(Radhakrishnan et al., 1993), 29 (Craig et al., 2001), 31 (Wall and George, 1991), 35 (Galvin and Van Stavern, 2004) and 36 years. (Mezaal and Saadah, 2005)

The condition does occur in childhood, although no large epidemiological studies in this group of patients have been carried out. It is rare in prepubertal children and has different characteristics to the adult form, including no apparent predilection for obese females. (Cinciripini et al., 1999; Rose and Matson, 1967) Amongst older teenage children, however, the rates of obesity seem to mirror those of the adult IIH population (Rowe and Noonan, 2002). A meta-analysis in 2007 confirmed these findings. (Genizi et al., 2007) Amongst the 244 children included in the analysis, the percentage of females was 45% in children aged 0-11 and 70% in those aged 12-18. Corresponding rates of obesity were 26% amongst the younger children and 64% for the older group. Younger children with IIH appear to represent a unique group, leading to the possibility of different mechanisms underlying the childhood form of the disease.

1.1.3.3 Racial and Genetic factors

Ethnic background has not been shown to affect the incidence of IIH, although few studies have addressed this question or involved sufficient numbers of patients. In Wall and George's study (1991) of 50 patients, 31 were black and in the Detroit study of 77 patients,

race was documented in 74, with 50 African-Americans and 24 Caucasians recorded. (Galvin and Van Stavern, 2004) A series of 450 patients studied over 17 years by Bruce et al (2008) comprised 246 (55%) white, 197 (44%) black, 5 (1%) Hispanic and 2 (<1%) Asian patients. However, in these American studies, numbers may simply reflect the ethnic composition of the source population. Small case reviews have confirmed that IIH occurs in Chinese and Korean populations, (Hung et al., 2003; Tae Wan Kim, 2008) although conclusions about IIH incidence specific to these ethnic groups are also precluded by small study size.

There is little to suggest a genetic predisposition or inheritance pattern in IIH. It has been reported in female homozygous twins, but the patients were both shown to have slightly large lateral ventricles, suggesting the possibility of hydrocephalus. (Fujiwara et al., 1997) Other isolated case reports of familial presentation have appeared in the literature, including a Croatian family in which six of 15 members studies were affected by IIH, although three did not have lumbar puncture to confirm elevated CSF pressure. (Karaman et al., 2003)

In a review of 237 US patients with IIH, 11 families were identified in which two or more members had a confirmed diagnosis of IIH. In 11 families the relationship was parent to child, in four, sibling. (Corbett, 2008) Obesity was present in 85% of all 27 subjects, which may explain the apparent family connection. The authors of this small study suggest that screening of first degree relatives of patients with IIH may be of value, although screening for other obesity-related conditions could equally have been the recommendation.

1.1.3.4 Body Mass

Early publications recognised the association of obesity with the clinical syndrome later named as IIH. Foley's paper (1995) on 'toxic hydrocephalus' commented that 14 out of 60

patients were ‘conspicuously obese’. Greer (1965), wrote of obesity in all of 20 female patients with ‘benign intracranial hypertension’ studied in a US case series, five of whom reported a gain in weight of 10 to 30lb in the six months preceding the study, and recommended weight reduction as the most effective long term treatment.

The evidence linking IIH and obesity is now conclusive. Published rates amongst IIH patients of obesity, defined as body mass index (BMI) above 30kgm^{-2} include 71% (Radhakrishnan et al., 1993) 88% (Galvin and Van Stavern, 2004) and 91%. (Kesler and Gadoth, 2001) The mean weight of patients in Durcan and Corbett’s (1988) population study was 38% above that considered ideal body weight. In the North American prospective study of 50 patients by Wall and George,(1991) 47 were obese according to standard definitions and there was an average weight gain over the 12 months preceding the onset of symptoms of 7.7 kilograms. Likewise, the Benghazi case-control study showed that not only were 40 IIH patients significantly more overweight compared to 80 controls, but that 24 of the patients had gained over 10 kilograms in weight in the 12 months prior to diagnosis compared to only six in the control group. (Radhakrishnan et al., 1993)

Even moderate weight gain appears to be associated with IIH. Patients with BMI of 25-30 had an increased risk of IIH in a recent US case-control study, although higher categories of BMI were associated with progressively greater risk of the condition. (Daniels et al., 2007) In the same study, 29% of patients reported no gain in weight and it is important to note that IIH does occur in people who have normal or even low body mass, albeit less frequently.

1.1.4 Associated Factors

With the exception of female gender and obesity, there are no proven associations in IIH. A variety of conditions and medications have been linked with the disease over the years, but whether the clinical syndrome occurs as a result of, or is simply a chance association with the factor in question is impossible to prove. Furthermore, the description of associated conditions in the context of a disease termed 'idiopathic' seems fraught with contradiction. Nevertheless, certain factors have been reported in association with IIH with sufficient frequency to warrant further attention.

1.1.4.1 Vitamin A

The fat soluble vitamin retinol (Vitamin A) is known to affect the structure of the arachnoid villi, the thin walled structures that project into the blood-filled sinuses of the dura and permit flow of cerebrospinal fluid (CSF) from the arachnoid space into the bloodstream. Studies of retinol-deficient animals have demonstrated raised CSF pressure although the exact relationship between the structural changes in the arachnoid granulations observed and the mechanism of raised pressure is uncertain. (Hayes et al., 1971) Cases have been reported of intracranial hypertension occurring in infants deficient in vitamin A, which resolved with replacement therapy. (Keating and Feigin, 1970)

Excessive dietary intake of vitamin A has also been associated with raised intracranial pressure. Historical narratives of Polar Eskimos and their dogs suffering from the clinical features of intracranial hypertension, including headache and prostration, after ingesting large quantities of liver from polar bears were later linked to the high levels of vitamin A in the organ.(Fishman, 2002) A case was reported in 2000 of IIH in a patient who consumed

excessive quantities of raw carrots, rich in retinol, and improved clinically when her carrot intake ceased.(Donahue, 2000) The effects of vitamin A intoxication, comprising systemic disturbance as well as intracranial hypertension, have been further revealed through the increasing therapeutic administration of retinol-containing compounds for dermatological and other conditions, but the mechanism of the raised pressure has yet to be determined.

Elevated retinol levels in patients with IIH have been demonstrated in a small number of specifically designed studies, summarised in table 1.3.

Table 1.3 Published Studies of Vitamin A in IIH

1st Author	*Year*	*Numbers*	*Methods*	*Findings*
Jacobson	1999	16 IIH Patients 70 Controls	**Serum** retinol and retinol esters quantified by chromatography	Significantly higher serum retinol in IIH patients, no differences in retinyl ester levels
Selhorst	2000	58 IIH Patients 40 Controls	**Serum** retinol by fluourometric method (+Serum retinol binding protein (RBP) in 30 patients & 17 controls)	RBP *but not* retinol significantly higher in IIH
Warner	2002	20 IIH patients 58 Controls	**CSF** retinol levels measured by chromatography	CSF retinol significantly higher in IIH patients vs controls
Tabassi	2005	20 IIH Patients 20 Controls	**Serum** and **CSF** retinol analysed by chromatography	CSF *but* <u>*not*</u> serum levels significantly higher in patients than controls

The finding of raised concentrations of serum retinol caused speculation about a non-specific alteration in retinol metabolism contributing to IIH in predisposed individuals. (Jacobson et al., 1999) Although Selhorst et al (2000) found elevated levels of retinal binding protein in patients with IIH compared to controls, the lack of significantly elevated retinol

levels in the same patients suggested the alteration may lie in the transport mechanism. Warner et al (2002) were the first researchers to show elevated retinol in the CSF of some patients with IIH, although corresponding serum levels were not measured to assess the ratio between blood and CSF levels. When this was addressed by Tabassi and colleagues, (2005) CSF retinol levels were significantly higher in the IIH patients than in 20 controls, but serum levels did not differ between the two groups.

There is enough data from studies to date to suggest that further study of the role of retinol in intracranial pressure is indicated. Clearly, not all patients with IIH show abnormalities of retinol metabolism, but there may be a subset of patients in whom it plays a pathophysiological role.

1.1.4.2 Medication

Case reports have implicated several drugs in intracranial hypertension (see table 1.4).

Table 1.4: Medication reportedly associated with intracranial hypertension

Endocrine:
Corticosteroid withdrawal
Levonorgestrel
Danazol
Tamoxifen
Growth Hormone
Anabolic steroids
Antibiotics
Tetracycline and derivatives
Nalidixic acid
Nitrofurantoin
Non-steroidal anti-inflammatories
Indometacin
Rofecoxib
Vitamin A
Retinol
Retinoids
Others
Lithium
Cimetidine

There have been many reports of IIH occurring in patients taking tetracycline-class antibiotics, including minocycline (Chiu et al., 1998, Kesler et al., 2004a) and doxycycline.(Lochhead and Elston, 2003) In a case-control study, self-reported use of tetracycline-class antibiotics was recorded in six of 34 patients compared to one of 41 controls.(Daniels et al., 2007) The authors used a regression model to demonstrate an association between IIH and use of the drugs within six months of symptom onset within the cohort. Other prospective, case controlled studies have failed to firmly establish a causative relationship. (Durcan et al., 1988; Giuseffi et al., 1991)

Abrupt withdrawal of corticosteroid therapy has been reported to cause a syndrome indistinguishable from IIH, in which clinical improvement follows reintroduction of the drug. (Neville and Wilson, 1970) This has not been conclusively shown in more recent controlled studies of IIH defined according to strict diagnostic criteria. (Giuseffi et al., 1991)

The oral contraceptive pill has been historically connected with IIH. Later, specifically designed studies found no significant differences in the numbers of women taking exogenous hormonal medication in patients with IIH compared with control subjects or the general population.(Durcan et al., 1988; Ireland et al., 1990; Giuseffi et al., 1991) It is conceivable that earlier publications included undiagnosed cases of cerebral venous sinus thrombosis, incorrectly labelled as IIH, amongst women taking hormonal medication, which may have led to false assumptions about an association. Glueck et al (2005) reported a series of 65 women with IIH who had, with one exception, normal cerebral venography, in which 24 (37%) were taking or had recently taken oral contraceptive or exogenous oestrogens. Such studies continue to influence popular view regarding an association, such that it

appears to be common clinical practice for women with IIH to be advised to avoid or withdraw hormonal medication.

1.1.4.3 Pregnancy

Pregnancy was traditionally regarded as causing an increased risk of IIH. Greer (1965) described eight cases of women with symptoms of benign intracranial hypertension between the first and fourth months of gestation. It was observed that the duration of their illness was brief in comparison to cases in non pregnant women, suggesting some relation to the rapid changes in levels of oestrogen and corticosteroid levels.

In 1984, a retrospective case control study and literature review concluded that the apparent association with pregnancy reflects the age and gender of the typical patient with IIH.(Digre et al., 1984) Further rigorous investigation has failed to show any statistically significant relationship, with similar pregnancy histories amongst IIH patients and matched controls.(Durcan et al., 1988; Ireland et al., 1990) As with the use of oral contraceptive medication, a high prevalence of pregnancy is to be expected in a condition favouring women of reproductive age.

1.1.4.4 Menstrual Dysfunction

A history of menstrual irregularities does appear to be more common in IIH than in unaffected females. In one questionnaire study of 40 IIH patients, a change in menstrual pattern just prior to diagnosis was more frequently reported than in the reference period in 39 controls. (Ireland et al., 1990) Age of onset of menses at or before age 13 years was also significantly more likely amongst case subjects.

Menarche, oligomenorrhoea or amenorrhoea have preceded the onset of IIH in case reports (Greer, 1964) and larger studies have listed menstrual dysfunction amongst reported symptoms, (Foley, 1955; Durcan et al., 1988; Glueck et al., 2005; Kleinschmidt et al., 2000) There has been no published evidence of specific hormone dysfunction to explain these findings and it is worth noting that obesity itself is known to be associated with menstrual irregularities.

1.1.4.5 Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) appears to occur with increased frequency in IIH. In the study by Glueck et al, (2005) 37 (57%) of the 65 women with IIH were found to meet the diagnostic criteria for the syndrome. Two years previously, the same researchers had reported the syndrome in 15 (39%) of a separate cohort of 38 patients with IIH. (Glueck et al., 2003) Whilst this would appear to represent a much higher prevalence of PCOS than that of the general population, the high levels of obesity in both IIH cohorts and the lack of reliable data on the incidence of PCOS amongst a similarly obese population make conclusions difficult to reach.

1.1.4.6 Sleep Disorders

Sleep apnoea syndrome (OSA) is also prevalent amongst an obese population, but several recent papers have linked it with IIH. Purvin et al (2000) investigated four patients who had papilloedema and OSA. Although CSF pressure was normal on a daytime lumbar puncture in all, the one patient who had overnight intracranial pressure monitoring showed significant elevations in pressure accompanying periods of apnoea and arterial oxygen desaturation. A year later, Marcus et al (2001) reviewed 53 patients with IIH, 37 of who reported symptoms

of sleep disorder. Polysomnograms were carried out in 14, confirming OSA in six cases. Lee et al (2002) carried out a prospective, multi-centre review over five years of male patients with IIH and identified six cases of OSA amongst 18 men meeting the full diagnostic criteria for IIH. In the largest published series of IIH, Bruce et al (2009) confirmed OSA in 25 (4%) of 655 women and (16) 24% of 66 men. It is possible that this retrospective series may have underestimated the prevalence of the condition, since many men in the study did not undergo sleep studies. It remains unclear whether there is a disease association between OSA and IIH, or if OSA plays a causative role in the condition, such that intracranial hypertension secondary to OSA is a separate clinical entity to 'true' IIH.

1.1.4.7 Anaemia

The most recent diagnostic criteria for IIH specify severe iron deficiency anaemia as a condition that can masquerade as IIH. (Friedman and Jacobson, 2002) Biousse et al (2003) reviewed the English and French literature and found 30 cases in which signs of isolated raised intracranial pressure (ICP) were associated with anaemia. Unfortunately, in many cases, CSF opening pressure was not recorded nor cerebral venous sinus thrombosis excluded. Most recently, Bruce et al (2009) reported anaemia of less than $12gdl^{-1}$ in 56 (9%) of women and 3 (5%) of 66 men with IIH. There have been further examples in medical literature to suggest more than an incidental association between IIH and iron deficiency anaemia, but controlled studies have yet to prove any causal relationship. (Tugal et al., 1994) A retrospective consecutive case series at the Birmingham and Midland Eye Centre, UK, between 2005 and 2007 of 107 new cases of IIH according to strict diagnostic criteria found six instances of microcytic anaemia, with haemoglobin levels below $10.2gdl^{-1}$. (Mollan et al.,

2009) The prompt resolution of symptoms and improvement in visual function upon correction of the haematological abnormality in all cases was highly suggestive of an association between anaemia and raised intracranial pressure. Testing patients who present with signs of IIH to exclude anaemia is recommended.

1.1.4.8 Other Co-morbid Conditions

Systemic arterial hypertension has been reported as occurring in 14 to 32% of patients with IIH.(Wall and George, 1991; Galvin and Van Stavern, 2004; Ireland et al., 1990; Kesler and Gadoth, 2001) In one study, blood pressure was significantly higher amongst people with IIH than matched controls.(Ireland et al., 1990). Hypertension was reported in 21% of women and 24% of men in the review by Bruce et al. (2009) Whether there is a true disease association or simply a reflection of the high incidence of elevated blood pressure amongst a population with increased body weight is unclear.

Other co-morbid conditions associated with IIH include diabetes mellitus, thyroid disease, hypoparathyroidism, stroke, chronic migraine, ulcerative colitis and systemic lupus erythematosus.(Durcan et al., 1988; Wall and George, 1991; Galvin and Van Stavern, 2004) There are published examples of apparent IIH occurring in patients with a variety of other conditions, including hepatitis A and E,(Thapa et al., 2009a; Thapa et al., 2009b), transplanted kidneys (Durcan et al., 1988) leukaemia, (Vartzelis et al., 2009) and the lysosomal storage disease cystinosis, (Dogulu et al., 2004) although a complex drug history often complicates the picture. Similar to the numerous proposed associations of medication with IIH, the prefix idiopathic is questionable when the condition can reasonably be assumed to be the sequel of a recognised underlying disease.

1.1.5 Clinical Features

1.1.5.1 Headache

Headache has consistently been shown to be the most common symptom of IIH, occurring in 68 to 98% of patients (Wall and George, 1991; Radhakrishnan et al., 1993; Kesler and Gadoth, 2001) and featuring as the presenting complaint in many. (Durcan et al., 1988) It appears to be less common amongst children with the condition, who may frequently present with other signs such as irritability or visual failure. (Lim et al., 2004)

In a prospective study comparing 50 people with IIH and 100 control subjects, headache was shown to occur frequently in both groups, but it was the daily occurrence of headache that differentiated IIH patients from controls. (Giuseffi et al., 1991) The headaches show variation in their clinical features and may be indistinguishable from other headache types such as migraine and tension-type headache. (Mathew et al., 1996) Friedman and Rausch (2002) studied a cohort of 82 patients with IIH and found 68% meeting the diagnostic criteria for primary headache as defined by the International Classification of Headache Disorders, ICHD-1. The headaches were divided as tension-type in 30%, migraine without aura 20%, chronic tension-type headache 10% and analgesia overuse in 8%. Isolated cases of cluster headache in association with IIH have also been reported. (Volcy and Tepper, 2006; Testa et al., 2008) One small, retrospective study found that patients were divided according to whether they had throbbing, migraine-like headaches (6 out of 16 IIH patients) or oppressive, heaviness headaches (9 out of 16). (Volcy-Gomez and Uribe, 2004) In the study by Wall and George, (1991) 39/50 patients said the headache was pulsatile, 41 said it was different from previous headaches and 44 felt it was the worst headache they had ever

experienced. A questionnaire study by the same author found in 63 patients that the headache occurred daily in 74% and often had features of presence on wakening and pain in a nerve root or retro-ocular distribution. (Wall, 1990) A further study showed ocular pain to be a much more predominant feature in patients with IIH than controls. (Daniels et al., 2007) Other researchers found that the headache of IIH can be unilateral, or generalised and may be worsened by coughing, straining or the Valsalva manoeuvre.(Corbett et al., 1982) Quite often, headache may be the only presenting symptom.(Galvin and Van Stavern, 2004)

1.1.5.2 Visual Disturbance

Disturbance of vision is the second most prevalent symptom of IIH. Visual symptoms usually accompany headache, but may occur in isolation, as found in 19.5% in one study of 77 patients.(Galvin and Van Stavern, 2004) A variety of symptoms are reported, including blurring, double vision or short-lived visual abnormalities. Transient visual 'obscurations', variously described as shadows, dark patches or black spots in the field of vision, affecting one or both eyes and resolving after a few seconds or minutes, are reported in 57 to 72% of patients. (Wall and George, 1991; Radhakrishnan et al., 1993; Kesler and Gadoth, 2001) They may occur with changes in posture. Both the exact pathophysiology and the prognostic significance of transient visual obscurations remain unknown. (Schirmer and Hedges, 2007)

Visual symptoms in the review by Bruce et al (2009) were divided into vision changes, transient visual obscurations and diplopia, with frequencies amongst 655 women of 20%, 11% and 5% respectively. Other eyesight abnormalities occur less frequently, and include diplopia and 'sparkles' (photopsia) or the sensation of flashes of light. Even less commonly

patients present with visual loss, although central vision is usually spared until late in the course of the illness. (Rowe and Sarkies, 1998)

1.1.5.3 Additional Symptoms

Intracranial noises occur frequently, usually described as 'whooshing' or 'roaring' in the ear. The sounds are often pulsatile. In prospective analyses, such noises occur in as many as 60% of patients. (Wall and George, 1991) Lower frequencies, such as 6% or less in some large series probably represent marked underestimation of symptoms by a retrospective approach. (Bruce et al., 2009; Giuseffi et al., 1991; Kesler and Gadoth, 2001) It has been proposed that tinnitus in IIH is produced as an effect of the raised CSF pressure on the vestibulocochlear nerve. (Kapoor, 2008b)

Nausea and vomiting may appear, reported in one prospective study in 40%. (Mezaal and Saadah, 2005) Signs of meningeal irritation sometimes occur, including neck stiffness and photophobia in addition to nausea.(Friedman and Jacobson, 2002) Rarer symptoms in adults also include shoulder, back, arm and radicular pain. Sense of smell may be affected, with hyposmia reported in some series. (Kapoor, 2008a)

In addition, psychological symptoms have been reported in IIH. Some patients complain of poor memory and mild generalised intellectual impairment has been found on neuropsychological testing in one study of 20 patients. (Sorensen et al., 1986b) Behavioural changes and disorders of attention and concentration have been reported in children with IIH. (Parness-Yossifon et al., 2008) There have been case reports of affective and dissociative disorders in patients with IIH although psychiatric illness may of course co-exist with IIH. (Duggal, 2005, Kuzman et al., 2008) One study compared social function and symptoms of

anxiety and depression amongst 28 patients with IIH to 30 weight-matched and 30 normal weight control subjects.(Kleinschmidt et al., 2000) IIH patients were significantly more depressed than normal weight but not weight-matched controls and had worse scores than all controls on many items of the Spielberger State-Trait Anxiety Inventory and Short Form 36 Health Survey (SF36). These findings mirror those of Daniels et al, (2007) who showed that vision-specific and overall health-related quality of life measures were affected to a greater extent in IIH than other neuro-ophthalmological disorders. They too concluded that obesity and weight gain seem to have the greatest effect on the mental health aspects of IIH. It is important to note also that patients with IIH may be entirely asymptomatic and present only after routine optician's tests reveal swollen optic discs.

1.1.5.4 Papilloedema

Papilloedema is almost a universal finding in IIH and its absence should cause the diagnosis to be questioned. Since the invention of the ophthalmoscope in the late 19th century, much has been written about the evaluation of papilloedema as well as the anatomical changes involved in optic disc swelling and their consequences. Grading of the severity of papilloedema is discussed in chapter 4.

1.1.5.4.1. Assessment of Papilloedema

Slight oedema of the disc may be difficult to detect using the direct ophthalmoscope, even when pupils are chemically dilated to allow visualisation of a greater portion of the retina, so examination with a slit lamp is required. This is a combination of a high intensity light source with a microscope and series of lenses to allow detailed examination of the structures of the eye via a magnified, 3-dimensional view. Stereoscopic retinal photography also produces a

stable, enlarged image of the optic disc which is easier to assess than the ophthalmoscopic view and forms a lasting record of the disc appearance for later comparison. In equivocal cases, fluoroscein angiography may be needed to display the leakage of dye from retinal vessels which is typical of papilloedema. However, this test involves the intravenous administration of fluorescein with a theoretical risk of complications and is avoided when possible.

Congenital, anomalous variations in the architecture of the optic nerve head may mimic papilloedema and cause further diagnostic confusion.(Friedman and Jacobson, 2002; Friedman, 2001) The diameter of the scleral opening impacts on the appearance of the disc margin, with smaller openings tending to blur the appearance. (Frisen, 1982) Eyes with congenitally blurred disc margins are reported to have certain morphological features that distinguish them from those with true papilloedema, such as sharp, glittering light reflexes and normal nerve fibre bundles when examined with red-free light. (Hoyt and Knight, 1973) Nevertheless, such patients often undergo extensive investigation before conclusions over the benign nature of the discs are reached. Discs can be misshapen, tilted or show excessive pallor. Some people have 'crowded' optic discs in which there is little or no physiological cupping (the empty space in the optic nerve surrounded by the optic nerve fibres, described by the cup to disc ratio). The optic nerve head is small in diameter with nerve fibre bundles tightly crowded at the border. One large Chinese study found an approximate incidence for the general population of 38 in 1,000, defining crowded discs as small with slightly prominent border and no signs of pathology. (You et al., 2008)

Drusen are white condensations of hyaline-like extracellular materiel situated in the optic discs. Although initially thought to be innocuous, drusen may be associated with visual

obscurations, visual field defects and even visual loss via ischaemic or occlusive events. They are thought to affect less than 1% of the population (Lorenzen, 1966) and may be inherited, seen in young patients or acquired with age. Giant forms may occur and haemorrhage may accompany drusen in the deep papillary region beneath the retina or in the substance of the optic disc.(Sanders et al., 1970) Superficial deposits of hyaline are easy to detect on the disc surface, but when buried deeper in the substance of the nerve, they may cause dome-shaped elevations closely resembling papilloedema. (Acaroglu et al., 2002) Even greater difficulty arises if papilloedema occurs in addition to the presence of pre-exisiting optic nerve head drusen.

Certain features are said to help with the discrimination of optic nerve head drusen from papilloedema, such as visible blood vessels at disc margins, a sharp peripapillary nerve fibre layer, elevation confined to the disc and a small, cupless disc. (Acaroglu et al., 2002) In some cases however, additional imaging techniques are required to assist in the diagnosis. Ultrasonography of optic nerves has been widely available for some time and various types of apparatus are in use. The reflectivity of the nerve is low compared to that of the sheath and this led to the successful introduction of the A-scan technique during the 1970s. (Ossoinig, 1979) The later transorbital B-scan approach allowed a distance behind the globe to be chosen to consistently measure the nerve diameter. (Hansen and Helmke, 1996) Three-dimensional coronal C-scan ultrasound imaging with computerised reconstruction is also now available as an accurate and inexpensive tool for optic nerve measurement. (Garcia et al., 2004). Ultrasound can be a rapid, non-invasive way of detecting drusen, which appear as reflective, foreign-body type lesions due to their calcium content. Traditional CT scans will also detect their presence, but involve ionising radiation. Optical coherence tomography

(OCT) is an imaging modality analogous to ultrasound, but using time of flight of light instead of acoustic waves. (Hu et al., 2008) The axial resolution in retinal tissue is much greater than that of ultrasound or CT scans. Confocal scanning laser ophthalmoscopy is an alternative technique for obtaining topographic retinal images. (Mulholland et al., 1998) The Heidelberg Retinal Tomograph uses a scanning diode laser to rapidly acquire an image of the nerve head as a series of aligned, transverse sections and has a high sensitivity for detecting small changes in optic disc volume. Although not yet widely used in clinical practice, such imaging appears to have a role in the evaluation of papilloedema and IIH.

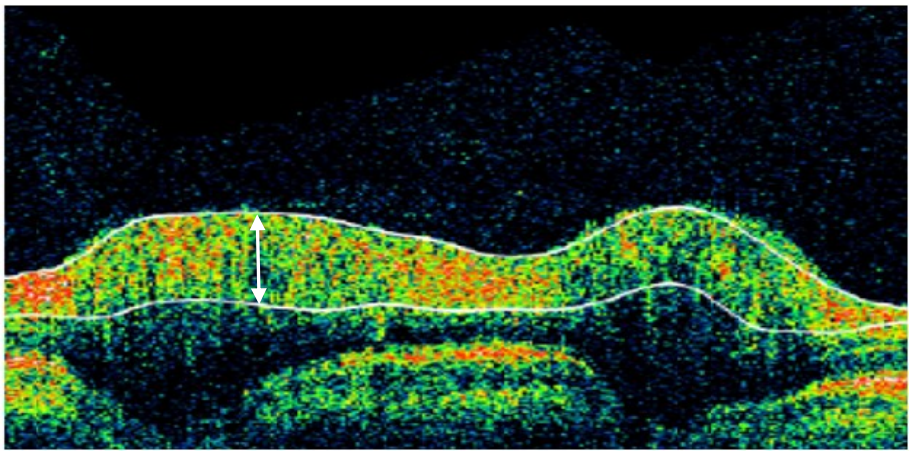


Figure 1.1 Optical Coherence tomography used to create a cross sectional image of the optic nerve. A colour scale is used to represent the intensity of the reflected coherent light waves. The arrow marks the distended peripapillary retinal nerve fibre layer. Image courtesy of Dr A.J Sinclair.

1.1.5.4.2 Pathogenesis of Papilloedema

The term papilloedema describes swelling due to raised intracranial pressure of the optic nerve head, or optic disc, the location in the eye where the optic nerve and retina connect. The main arterial supply to the anterior optic nerve is via the posterior ciliary arteries, with some supply of the more superficial part by the branches of the central retinal artery, with drainage almost exclusively via the central retinal vein and its tributaries, then into the

cavernous sinus. (Mackenzie and Cioffi, 2008) Papilloedema in brain tumours was initially thought to be a consequence of pressure on the cavernous sinus causing congestion of the ophthalmic vein and subsequent oedema of the optic nerve head. (Von Graefe, 1860) Later, electron microscopy studies showed that axonal swelling and not vascular disturbance was more likely to be the major factor. (Tso and Fine, 1976) Studies of experimental papilloedema in primates demonstrated prominent swelling and anatomical disruption of axons, confined to the surface nerve fibre layer of the optic nerve and anterior part of the prelaminar optic nerve head, but no vascular leakage. (Tso and Hayreh, 1977a; Tso and Hayreh, 1977b) Axonal degeneration but not swelling was seen in the myelinated retrolaminar optic nerve, where abundant extravasation was observed. The authors acknowledged that such features could be caused by a variety of pathological events, including mechanical crushing of the nerve, malignant hypertension and cyanide poisoning, thus were not specific for raised intracranial pressure. Additional studies showed disturbance of axoplasmic transport to be one of the major events in papilloedema due to a variety of conditions sharing a final common pathway.

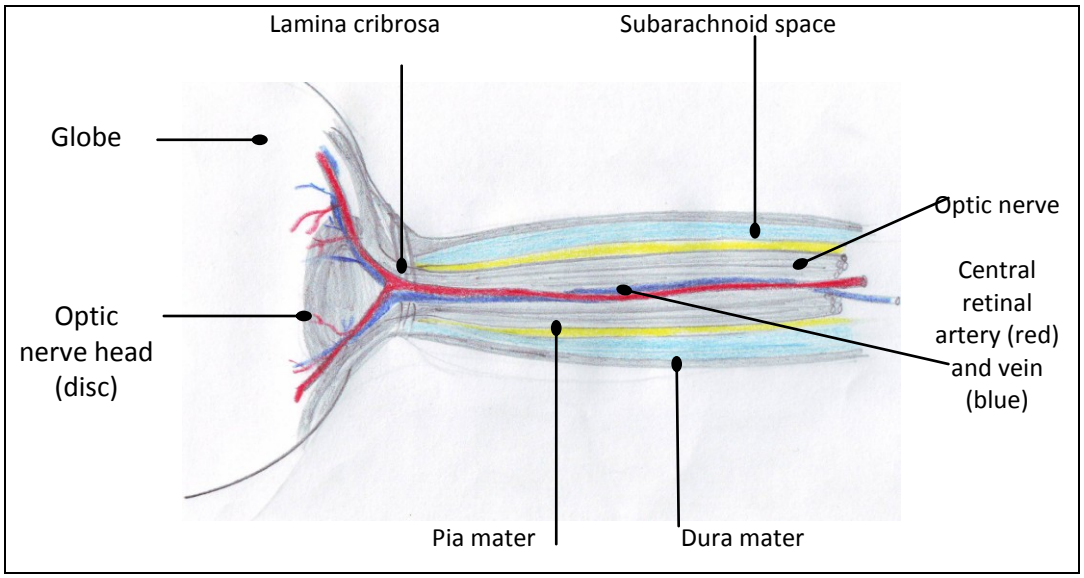


Figure 1.2: Cross section of globe and optic nerve showing brain membranes

Astrocytes are the predominant cell type in the optic nerve head, tightly packed into spaces between collagenous beams and extending processes into bundles of axons. The optic nerve is regarded as a prolongation of brain substance, rather than an ordinary cerebrospinal nerve, due to its unique anatomy. As it passes from the brain to extend to the orbit it receives sheaths from the three cerebral membranes, pia, arachnoid and dura mater, in a 'cul-de-sac' arrangement (Figure 1.2). It is surrounded by CSF throughout its length and its subarachnoid space is in direct communication with that of the brain, thought for many years to be free and bidirectional in nature. More recently, studies have challenged this assumption and led to the concept of compartmentation of the subarachnoid space in the optic nerve. (Killer et al., 2003) Differences in the concentration of beta-trace protein have been detected between spinal CSF obtained at lumbar puncture and CSF from the optic subarachnoid space. (Killer et al., 2006) In addition impaired communication of CSF between intracranial and optic nerve subarachnoid spaces has been demonstrated by a study of three patients with IIH who received intrathecal contrast medium then underwent CT-cisternography. (Killer et al., 2007) The concept of separation of the optic nerve subarachnoid space from the other compartments of CSF may help to explain the asymmetry of papilloedema seen in some patients with IIH.

1.1.5.4.3 Asymmetric Papilloedema

Discs with markedly different appearances are not rare and truly unilateral papilloedema does occur in IIH. An example is shown in Figure 1.3

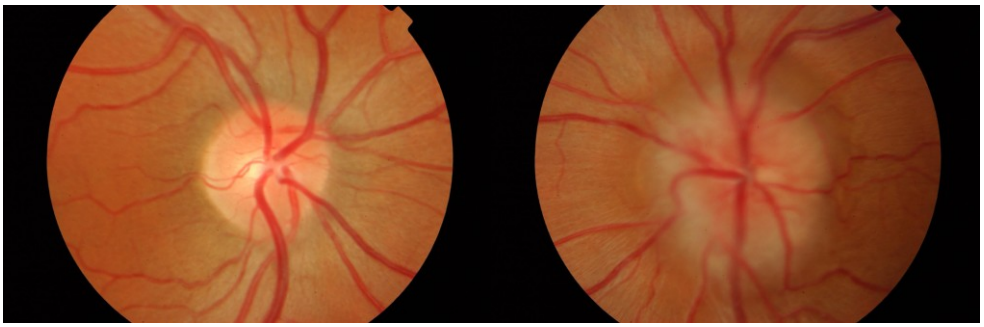


Figure 1.3: Asymmetric papilloedema in a 42 year old woman with IIH. The right fundus shows no papilloedema, the left fundus shows marked swelling of the optic disc.

Foley (1955) noted 'conspicuously unequal' papilloedema in three instances in his report of 60 patients. Unilateral papilloedema was seen in four of 57 patients in one more recent series(Corbett et al., 1982) and highly asymmetric papilloedema in six of 26 patients with IIH in another. (Lepore, 1992)

Any of three factors, high CSF pressure, low intraocular pressure and low perfusion pressure, can lead to axoplasmic flow stasis and papilloedema. (Wall and White, 1998) Hence existing vascular disease or ocular conditions such as glaucoma provide a theoretical explanation for the asymmetrical disc swelling. However, these factors can be excluded in most cases, leaving CSF pressure to explain the phenomenon. (Kirkham et al., 1973) Animal studies as well as the response in humans to surgical procedures demonstrate that papilloedema resolves or lessens when raised pressure in the optic nerve sheath is reversed. Thus it seems likely that asymmetric papilloedema reflects asymmetry in the optic nerve sheath. Differences in the structure of the optic nerve sheath subarachnoid spaces adjacent to the optic canals, where the diameter of the nerve is narrowest, could affect their response to elevations of intracranial pressure, causing differences in local pressure at the optic nerve heads. (Wall and White, 1998)

1.1.5.4.4 IIH Without Papilloedema

In 1972, a case report was published of an obese woman with severe headache, bilateral sixth nerve palsies and elevated CSF opening pressure, but whose fundoscopic assessment showed optic discs with defined borders and the presence of venous pulsations. (Lipton and Michelson, 1972) This may have been the first reported case of 'pseudotumour cerebri with no papilloedema'. Since then, a body of evidence has grown for a distinct variant of IIH in which papilloedema does not occur.

Marcelis and Silberstein (1991) described ten patients fulfilling the diagnostic criteria for IIH and reporting headaches with migrainous features, who did not develop papilloedema at any time during a follow-up period of up to ten years. The authors speculated that possible mechanisms for the phenomenon included bilateral defects of the optic nerve sheath, either congenital or acquired, or elevations of the intracranial pressure that were intermittent and insufficient to produce disc swelling.

Mathew et al (1996) performed lumbar punctures in 85 patients with refractory migraine and found 12 patients had CSF opening pressures above 270mm water. None had papilloedema, visual obscurations or diplopia. This led to a call for all patients with treatment-resistant headache and migrainous features to have CSF pressure measurement, to exclude a diagnosis of 'Idiopathic Intracranial Hypertension Without Papilloedema (IIHWOP).' In 1998, Wang et al (1998) conducted a case-control retrospective study of 85 patients with intractable chronic daily headaches, normal neurological examination and no papilloedema, all of whom had also undergone lumbar puncture. In 25 patients, the pressure was above 240mm on at least one occasion, leading to the diagnosis of IIHWOP. In comparison with the control group (60 patients with normal CSF pressure), the IIHWOP

cases had significantly higher incidences of pulsatile tinnitus, blurred vision and increased BMI.

Further small series describing IIHWOP have been published subsequently, including paediatric case reports. (Wraige et al., 2002; Winner and Bello, 1996) More recently a Brazilian study reported six cases of IIHWOP amongst 61 patients with chronic migraine consecutively investigated with imaging and lumbar puncture. (Vieira et al., 2008) The CSF opening pressures amongst the six cases were not greatly elevated, ranging from 242 to 300mm, with three values below 250mm. Confidence in the diagnosis of IIH was attributed by the authors to the clinical outcomes and headache response to lumbar puncture; improvement was seen in all six cases.

The International Classification of Headache disorders 2nd edition (ICHD-II) now acknowledges that whilst the majority of patients with IIH do have papilloedema, a variant without papilloedema can be observed. An estimated prevalence for IIHWOP of 5.7% was reported from a cross-sectional analysis which identified 20 patients from a total of 353 neuro-ophthalmology patients seen in a Utah University department between 1990 and 2003. (Digre et al., 2009) Whilst all patients studied had elevated CSF opening pressure, the mean value for the IIHWOP cohort was slightly lower (309mm v 373mm, p=0.031). Visual fields at presentation were normal in 73% of IIHWOP patients compared with 13% of controls (p=0.002). Bilateral daily headaches affected both groups similarly, but aura was a more common symptom amongst the IIHWOP group (p=0.035).

Whilst IIHWOP is now widely recognised, its diagnosis requires a high index of suspicion in addition to thorough neuro-ophthalmological assessment and careful CSF pressure measurement. The significance of a single CSF pressure measurement at lumbar puncture

has, as with all cases of IIH, been called into question in IIHWOP, due to potential variability of CSF pressure over time and the risk of both false positive and false negative values. Torbey et al (2004) call for the use of continuous CSF pressure recording in establishing the diagnosis of IIHWOP. In a retrospective review of ten patients with chronic daily headache, suspected to have IIHWOP on the basis of clinical presentation and opening CSF pressure above 200mm at lumbar puncture, the results of CSF pressure measurement via a lumbar catheter for 2.1 ±0.2 days were said to play a vital role, both in confirming the diagnosis of IIHWOP and supporting the decision to proceed to therapeutic surgical intervention. Four of the ten patients had lumbar puncture CSF pressures below 250mm, yet all patients had some abnormalities of the CSF waveform considered to be pathological, such that eight patients were referred for surgical CSF diversion procedures. The abnormalities were only detected during periods of sleep or rest, due to the frequent movement artefacts in the recordings at other times. The co-existence of normal baseline CSF pressure, (awake, resting pressures of below 204mm for all patients), with patterns of unstable elevated pressures is highlighted by this small study and no adverse events were reported. However, continuous CSF pressure monitoring is invasive and carries a significant risk of complications such as infection, thus rigorous prospective evaluation would be needed before it could be adopted as routine screening for IIHWOP.

1.1.5.5 Visual Impairment

Visual impairment is the main morbidity of IIH. Patients often fail to present with symptomatic visual loss so detailed assessment of visual function is required. Tests of colour vision are often recorded in routine clinical practice, but are seldom reported in published

studies. The prevalence of genetic colour vision deficiency in the general population may limit their use.

1.1.5.5.1 Visual Acuity

The refracted visual acuity is often normal when tested in patients with IIH. Reduced central visual acuity does occur, but review of the recent literature suggests this to be the case in less than a quarter of patients at presentation.(Wall and George, 1991; Radhakrishnan et al., 1993; Galvin and Van Stavern, 2004; Craig et al., 2001)

Loss of vision seems to occur via diffuse, ischaemic damage to the optic nerve fibres caused when the vascular supply of the nerve is compressed by swelling. (Wall and White, 1998) Preservation of central vision is thought to be due to the relative surplus of visual processing elements serving the central portion of the visual field, such that peripheral vision is more likely to be affected by diffuse damage to the optic nerve. Testing the best refracted visual acuity in both eyes, using standard letter charts, remains an important part of the assessment of patients with IIH, since if abnormalities are present, the degree of optic nerve damage can be considered substantial and indicative of the need for urgent treatment. Amongst patients with early loss of central vision, other causes such as optic neuritis and ischaemic optic neuropathy should be considered and excluded if necessary.

1.1.5.5.2 Contrast Sensitivity

Letter charts provide information about just one aspect of visual perception. Sensitivity to visual contrast using stimuli with a range of spatial frequencies can also be measured. The technique is based on patterns or gratings, ranging from coarse (low spatial frequencies) to fine patterns (high spatial frequencies.) Sinusoidal gratings are often used, in which the

luminance of alternating light and dark bars are varied in a sinusoidal fashion, with the spatial frequency corresponding to the number of pairs of light and dark bars per degree of visual angle. Specifically designed plates or computer generated images projected on a monitor are used to display the patterns.

An alternative to gratings is the Pelli-Robson contrast sensitivity chart. (Pelli et al., 1988) It consists of rows of letters of the same size but decreasing contrast. (Figure 1.4) Wall-mounted, it is normally viewed from a distance of one metre, from where the letters equate approximately to one cycle per degree, giving a measure of contrast sensitivity at one spatial frequency. Letters on the chart are organised into groups of three, i.e. triplets, there being two triplets per line. Within each triplet, letters have the same contrast. The contrast decreases from one triplet to the next, thus the difficulty increases line to line as well as in the middle of each line. Such charts have practical advantages although print quality must be calibrated and charts displayed according to precise guidelines to meet the standards required of a clinical instrument.

Contrast is best defined as the difference in luminance between the letter and background, divided by the luminance of the background. This ratio of luminances is known as the Weber contrast and differs from the Michelson contrast used for grating stimuli. The lowest visible contrast is called the contrast threshold, the reciprocal of which is the contrast sensitivity, using expressed as the Log_{10} contrast sensitivity. Thus the higher the Log_{10} contrast sensitivity, the better the person's vision and steps on the scale correspond to equal effects.

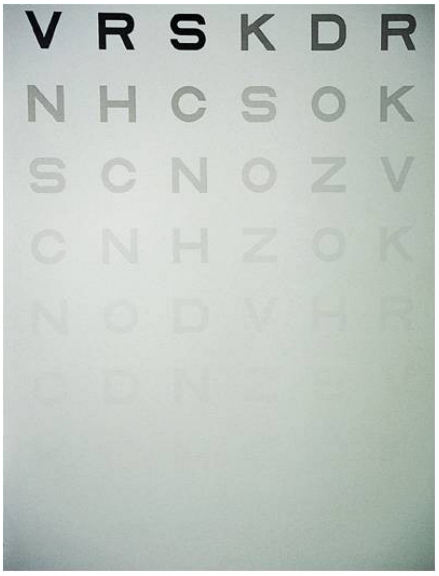


Figure 1.4: Pelli-Robson contrast sensitivity chart

Studies have shown that abnormalities in contrast sensitivity occur more frequently amongst patients with IIH than healthy control subjects.(Wall, 1986; Bulens et al., 1988) In IIH case series and prospective studies, abnormal contrast sensitivity occurs in significantly more patients at presentation than loss of acuity, and in some cases visual field loss, which has led to claims that it is a more sensitive measure of visual dysfunction.(Wall, 1986; Wall and George, 1991; Verplanck et al., 1988)

1.1.5.5.2 Visual Field Defects

Testing of visual fields by confrontation in patients with IIH may elicit few abnormalities, but formal perimetry reveals that visual field defects are often present and enlargement of the blind spot is nearly always seen. In general, visual field abnormalities are one of the earliest indicators of ophthalmic disease. Perimetry, the systematic examination and quantification

of the three-dimensional island of vision, has developed as an essential tool in their evaluation.

Kinetic perimetry involves a light stimulus of known intensity and size being moved to find the most peripheral location where it is seen by a person maintaining fixation on a central target. An examiner manually presents the light stimulus to the patient and records their response on a standardised chart. The result is a plot of several loci connected by a line called an isopter, defining a zone of equal visual sensitivity. Smaller and dimmer lights result in isopters closer to the centre where the visual threshold is lowest. Goldmann perimetry uses this method; examples are shown in Figures 1.5 and 1.6.

Static or automated perimetry involves the presentation by a computer of a brief static light stimulus at various loci throughout the visual field and recordings of the intensity of light at which it is seen. The Octopus Perimeter and the Humphrey Visual Field Analyser are both examples, with the latter now most commonly in use.(Werner, 1991) There are various test patterns for central, peripheral or full fields and a variety of screening strategies are possible. Software, such as the Statpac programme, is available to perform the screening and threshold tests as well as to aid in the interpretation of results. Visual thresholds are recorded in terms of decibels of attenuation, with lower thresholds having higher numerical value. Statpac compares the results of individual tests with normal population visual field data stored in the computer. Two values are calculated; the mean deviation (MD) is the average amount by which the measured threshold differs from the age corrected norm and the pattern standard deviation (PSD) is a measure of localised non-uniformity of the hill of vision. An example of automated perimetry is shown in Figure 1.7.

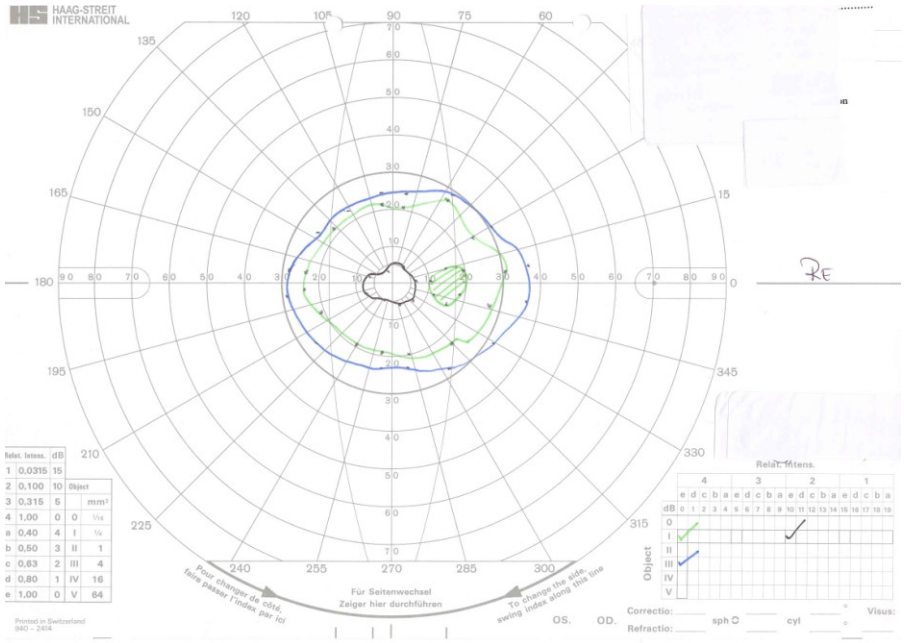


Figure 1.5: Visual field (Goldmann perimetry) from the right eye of a 54 years female with IIH showing marked constriction

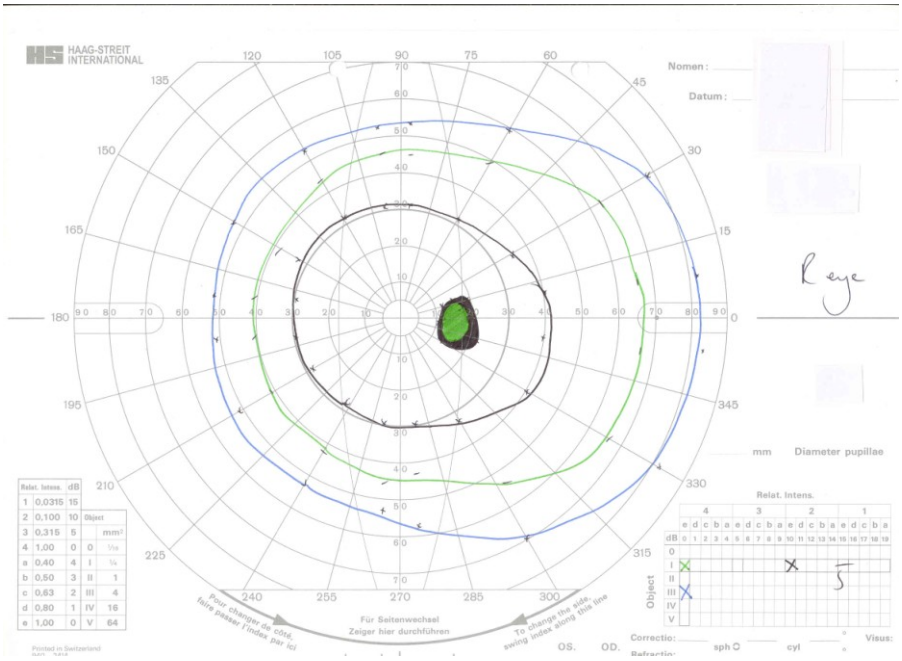
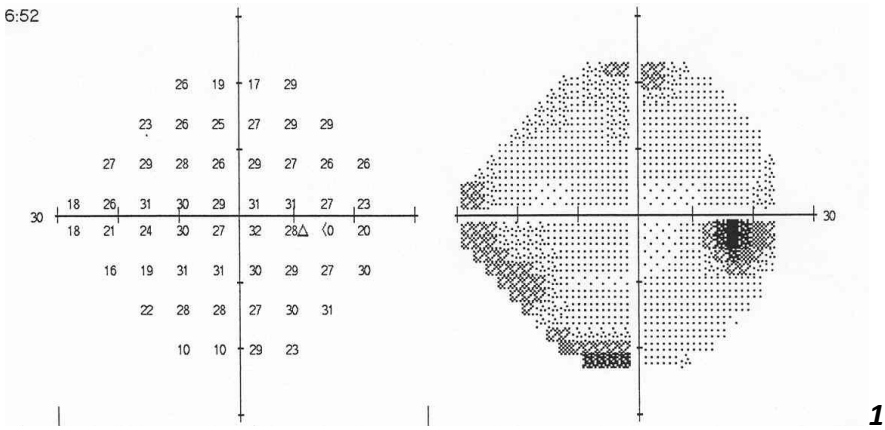


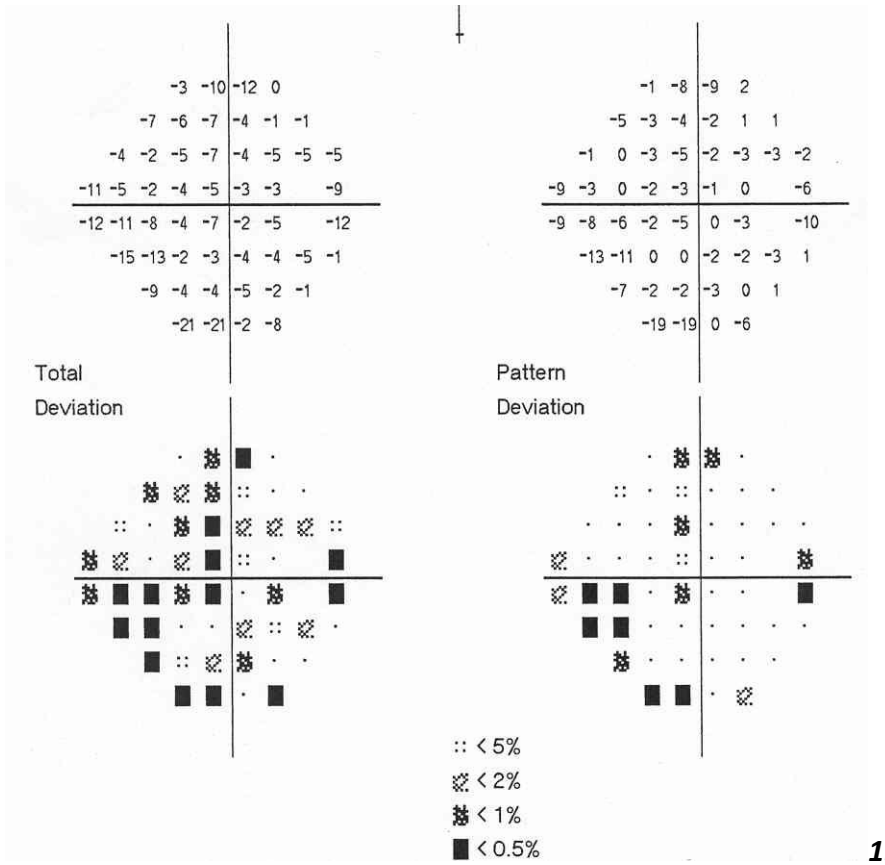
Figure 1.6: Goldmann fields with minor enlargement of the blind spot as the only abnormality

The Statpac software also monitors and records the patient's fixation on the central target during the test. Further measures of test reliability are provided by the recording of false negatives, when patients fail to respond to a light stimulus brighter than one previously responded to and false positives, in which patients respond to a stimulus that was not presented. Fatigue and inattention as well as volitional variability of response may lead to such errors. Even amongst technically acceptable visual fields, with low rates of false positives and negatives, variability may have a significant impact on their interpretation. In a large study of patients with ocular hypertension, retesting the visual fields failed to replicate abnormalities in the majority of cases. (Keltner et al., 2000) Abnormalities were not confirmed for 604 (85.9%) of the 703 originally abnormal and reliable visual fields when retests were carried out as part of the Ocular Hypertension Treatment Study. It is thought that a learning effect may influence the results of repeat perimetry and it is essential to confirm any abnormalities detected on an initial assessment. (Yenice and Temel, 2005)

Perimetry appears to be a sensitive test in IIH. At the initial visit in the study by Wall and George, (1991) Goldmann perimetry was abnormal in 87% of eyes and Humphrey automated perimetry in 92%. By comparison, abnormal Snellen acuity was present in only 22% of the same group of patients. Other large studies in IIH have documented similar rates, with automated perimetry tending towards greater sensitivity. (Rowe and Sarkies, 1998)



1.7a



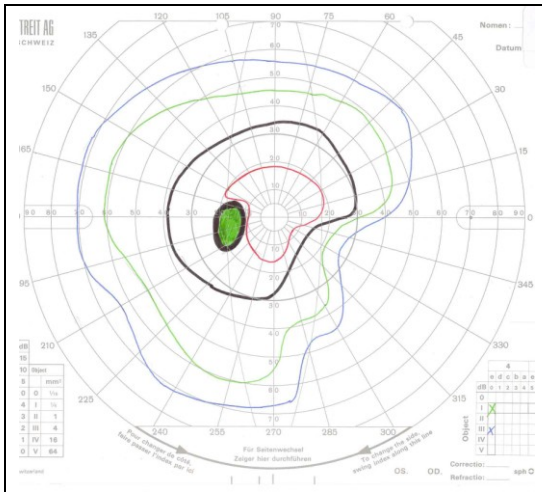
1.7b

Figure 1.7: Visual fields (Humphrey 24-2 automated static perimetry) from the right eye of a woman with IIH. Generalised reduction in sensitivity with enlargement of the blind spot and an inferonasal defect are shown. 1.7a: Visual thresholds as shown by greyscale diagram and numerical results; 1.7b: Numeric and symbolic representations of the calculated total and pattern response deviations from normal.

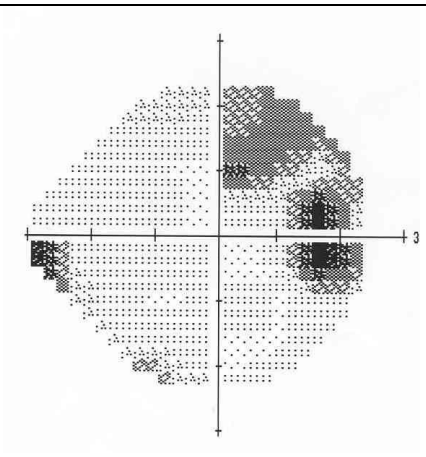
The visual field defects in papilloedema mirror those of other anterior optic nerve pathologies, such as glaucoma and anterior ischaemic optic neuropathy. Enlargement of the physiological blind spot is seen in most cases of IIH, related to the effect of the swollen optic nerve head occupying a larger area of retina (Figure 1.6). Often fields in IIH with blind spot enlargement are categorised with normal fields, unless they encroach on fixation, due to the benign and common nature of the finding. The locations of other visual field defects in IIH reflect the retinal nerve fibre arrangement and its relation to swollen areas of the optic disc. Of these 'disc-related' defects, peripheral rim constriction appears to be the most common (figure 1.5). Inferonasal steps are the next most common (figure 1.7), then arcuate scotoma, arch-shaped defects in the field of vision as well as nasal defects.(Rowe and Sarkies, 1998; Hung et al., 2003; Galvin and Van Stavern, 2004) Other less common defects include central, paracentral and caecocentral scotomata, with temporal and altitudinal losses even less frequently recorded. (Wall et al., 1991) (Figure 1.8)

Rather than providing extensive descriptions of the various field defects in series of patients with IIH, many researchers apply a grading system to group and summarise the findings. Wall and George (1991) published detailed grading systems for both manual and automated perimetry in their prospective study of 50 patients with IIH. Grades 0, 1, 2, 3, 4 and 5 were described in each, with 0 being normal visual field and 5, blinding visual field loss. This grading system has subsequently been adopted in several published studies in IIH. (Rowe and Sarkies, 1998; Celebisoy et al., 2007; Bruce et al., 2009) Interestingly, the grade of visual field defect did not correlate with the severity of papilloedema in the original description.(Wall and George, 1991) A later study by one of the authors did find that

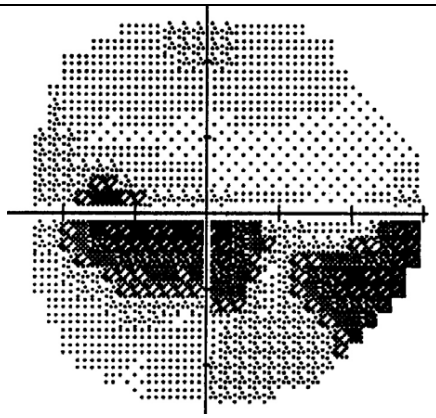
amount of optic disc oedema was related to the severity of visual loss, although there was considerable inter-individual variation. (Wall and White, 1998)



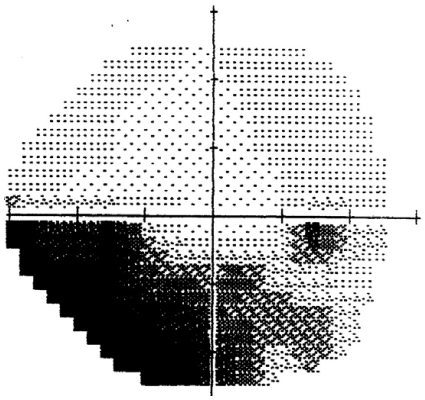
Nasal step left eye (Goldmann)



Temporal loss right eye (Humphrey)



Inferior arcuate and central scotoma left eye (Humphrey)



Moderate inferior arcuate scotoma right eye(Humphrey)

Figure 1.8 Examples of less common visual field defects in IIH

1.1.5.6 Additional Signs

It is a requirement of the modern diagnostic criteria for IIH that neurological examination is normal except for the presence of signs reflecting generalised intracranial hypertension and papilloedema.(Friedman and Jacobson, 2002) Unilateral or bilateral sixth cranial nerve palsies can therefore be expected and have been specifically documented in some studies at

rates of 17 to 33%.(Corbett et al., 1982; Radhakrishnan et al., 1993; Mezaal and Saadah, 2005) Abducens palsies are more likely to be unilateral and appear to be more common amongst children. (Johnston et al., 2007) Other cranial nerve defects have been reported very rarely, in single case reports, including facial and oculomotor palsies. (Bakshi et al., 1992; Capobianco et al., 1997)

Afferent papillary defects are also seen, although their frequency has not been formally reported in many studies. Wall and George (1991) found relative afferent papillary defects in nine patients. Rarer ophthalmological complications have been described, including choroidal neovascularisation (Castellarin et al., 1997) and metamorphosia, a visual distortion in which straight lines appear curved, normally seen in association with retinal folds. (Warner and Katz, 2005) A degree of optic atrophy, seen as small, pale optic discs, may be visible in some cases of IIH, where there has been prolonged papilloedema and optic nerve fibre loss.

1.1.6 Investigation

1.1.6.1 Imaging

Since IIH is largely a diagnosis of exclusion, patients presenting with signs and symptoms of raised intracranial pressure must be sufficiently investigated to rule out cerebral pathology and ventricular enlargement. Historically, plain skull X-rays and occasionally air encephalograms or ventriculograms were carried out. Whilst there are no pathognomonic radiological signs in IIH, an empty sella turcica and variable diminution in ventricular size have been frequently reported, although the latter has been debated. (Boddie et al., 1974) Computed tomography (CT) then became the investigation of choice until it was superseded

in recent years by magnetic resonance imaging (MRI). Posterior scleral flattening, relative to the normal curvature of the globe, prelaminar enhancement of optic nerves within the globe, vertical tortuosity of the orbital optic nerves and distension of the perioptic subarachnoid space, as well as empty sella, have recently been shown to be sensitive and specific markers of raised intracranial pressure amongst IIH patients in a restrospective MRI series. (Brodsky and Vaphiades, 1998)

To comply with the most recent diagnostic criteria, cerebral venous sinus thrombosis (CVST) must also be excluded. (Friedman and Jacobson, 2002) Thrombosis of the cerebral venous circulation can present with an identical clinical picture to IIH (Biousse et al., 1999) and may even fulfil the older 'modified Dandy' criteria for IIH. (Sylaja et al., 2003) It is possible to overlook sinus thrombosis on CT or MRI unless formal study of the cerebral vasculature is undertaken by computed tomographic venography (CTV) or magnetic resonance venography (MRV). (Lueck and McIlwaine, 2002) Thrombosis is usually recognisable on MRV if it affects the superior sagittal sinus, but the lateral and transverse sinuses are more difficult to assess as they display greater anatomical variation. (Higgins et al., 2004) There is some evidence that MRV may miss lesions in the transverse sinuses altogether and that direct retrograde cerebral venography may be a more thorough means of excluding defects. (Owler et al., 2003) Even more information may be gained through the use of manometry to reveal pressure gradients within the cerebral venous sinuses. Stenoses, or narrowings of the venous conduits have been demonstrated in some patients with IIH. (Farb et al., 2003) Thus, the 'gold standard' to exclude CVST is probably the combination of direct venography with manometric pressure measurement, but in current clinical practice, MRV or CTV are considered adequate.

1.1.6.2 Intracranial pressure measurement

The intracranial pressure (ICP) is usually measured by lumbar puncture examination to determine the pressure of the CSF. Although this is an indirect measure of the ICP, in contrast to direct measurement within the brain tissue or ventricles, it is believed to be an accurate reflection of the true intracranial pressure in conditions in which there is free circulation of the CSF. (Lenfeldt et al., 2007) The lumbar puncture examination is performed with the patient lying in the lateral decubitus position. A pressure recording of over 20 centimetres of water is generally considered to be abnormal. It is essential that the patient is as relaxed as possible and time should be allowed for the pressure to stabilise. The knees and hips should be in the extended position during pressure recording, since there is evidence that a flexed posture as well as the Valsalva manoeuvre can elevate the pressure. In one prospective study, 15 patients with various neurological disorders underwent lumbar puncture and measurement of CSF pressure. (Neville and Egan, 2005) Patients with an initial opening pressure of above 20cm were excluded. The mean resting pressure amongst the 15 patients was 14.6cm (range 10-19), which rose to 32.3 (range 26-47) cm when patients were asked to perform a Valsalva manoeuvre, with hips in flexion and bearing down against a closed glottis. All of the patients were thus able to elevate their pressure to levels that would normally be considered pathological. It is common practice for some lumbar punctures to be performed with patients in the seated position, particularly when the procedure is technically difficult due to patient obesity or other factors. Care is therefore needed in the interpretation of single recordings of CSF pressure to avoid over-diagnosis of intracranial hypertension.

There is considerable debate as to whether obesity itself is a cause of mildly elevated CSF pressure. A study of 134 patients diagnosed as having pseudotumour cerebri found an average CSF pressure, recorded by direct manometry, of 34.4 centimetres of water, compared to mean values of 13.6 and 16.7 amongst 15 non-obese and 41 obese controls respectively. (Corbett and Mehta, 1983) There was no correlation between CSF pressure and obesity, nor was the difference in pressures between the obese and non-obese controls significant when analysed statistically. Bono et al (2002) studied a group of 100 patients who were having lumbar punctures for diagnostic purposes, none of whom had papilloedema or abnormalities on MRI and MRV scans. No patient had a CSF opening pressure above 200mm. The obese subjects tended to have slightly higher CSF opening pressures but the differences were not significant. The authors concluded that a pressure above 200mm in a patient of any body weight was an indication for further investigation to exclude cerebral venous sinus thrombosis.

There is also a risk that lumbar puncture measurement of CSF pressure can fail to detect cases of intracranial hypertension. Continuous recording of CSF pressure has shown that the pressure changes over time, building up to a crescendo followed by sudden falls (Johnston, 1974) or reaching high, rapidly changing levels over 24 hours, which lack any particular rhythm and occasionally drop to normal values.(Gucer and Viernstein, 1978) Overnight monitoring in IIH shows that the baseline pressure is usually increased and that plateau or A waves (sustained above 50 mmHg for 5 to 20 minutes) and B waves (rhythmic, 5 to 50 mmHg, 0.5 to 2 cycles per minute) are often present. (Czosnyka and Pickard, 2004; Torbey et al., 2004) In theory, a single lumbar puncture may lead to normal pressure recordings in IIH. There is evidence that fluctuations in CSF pressure can occur in established IIH, such that

patients may have pressures within the normal range on repeat lumbar punctures despite the presence of symptoms and papilloedema. (Rabinowicz et al., 1968) However, practicalities and risks such as infection preclude the routine use of prolonged CSF pressure measurements and multiple lumbar punctures in routine clinical practice.

Attempts have been made to measure CSF pressure by other, less invasive methods. Intraocular pressure, measured by tonometry has been reported to correlate with intracranial pressure as measured by lumbar puncture. (Sajjadi et al., 2006) A later review found that the two measures did not correlate and suggested that variability in techniques of measurement as well as the various intra-ocular factors contributing to intra-ocular pressure could explain the differences. (Han et al., 2008) MRI and ultrasonography studies have suggested that the optic nerve sheath diameter can accurately predict raised intracranial pressure and that such measurement from imaging is feasible in the majority of patients. (Geeraerts et al., 2008a; Geeraerts et al., 2008b) However, any finding of optic nerve sheath diameters suggestive of intracranial hypertension would simply indicate a need for more precise measurement of pressure. Whilst it can be an uncomfortable procedure and alternatives would be welcomed, as yet there are no proven substitutes for lumbar puncture in IIH.

Analysis of the CSF in the patient with suspected IIH is mandatory, and its composition must be normal to conform to the diagnosis. CSF pleocytosis, indicating possible inflammatory conditions or infections, must be excluded. The only exception is that CSF protein content may be lower than the generally accepted normal of less than $0.4gl^{-1}$ in some patients with IIH. (Chandra et al., 1986)

1.1.7 Management

The goals of treatment in IIH are to reduce the elevated CSF pressure, preserve visual function and relieve symptoms. Combinations of medical, physical and surgical measures are commonly used.

1.1.7.1 Therapeutic lumbar puncture

Historically, repeated lumbar punctures formed the mainstay of treatment for many patients, using withdrawal of CSF to directly lower the intracranial pressure. Case series have reported the use of serial lumbar punctures, alone or in combination with other therapeutic interventions, with varying degrees of success. (Johnston et al., 2007) There have been no prospective trials however and it is not clear in many cases what the clinical consequences of not repeating the procedure would have been. It is widely believed that repeated lumbar puncture may result in a hole in the dura, maintaining lowered pressure via a small amount of chronic CSF leakage, but the prevalence of this phenomenon and its effect, if any, is entirely unknown. The removal of an average volume of 15-25 ml of CSF has been shown to be enough to reduce the pressure to below 10 cm of water, but in the same study, it took an average of only 82 minutes for the pressure to return to pre-drainage levels. (Johnston and Paterson, 1974)

The unpopularity of the procedure amongst patients as well as its uncertain clinical benefit has led to multiple lumbar punctures being largely phased out of current practice. In addition, the complication of post lumbar puncture low-pressure headaches may occur, which can be difficult to treat and might confuse the assessment of headache symptoms in IIH. There are certain instances in which serial lumbar punctures may still have a role. If

acute or rapidly progressive visual loss occurs in IIH, it may be essential to promptly reduce the pressure in an attempt to preserve vision via immediate drainage of CSF. Given the brisk restoration of CSF volume, this is unlikely to be a lasting solution, insertion of a lumbar drain being a more definitive approach, but lumbar puncture has the advantage of usually being simple and quick to perform. Lumbar punctures are also safe in the management of pregnant patients when temporary control of CSF pressure is required urgently and surgery or drug treatment is contraindicated. (Lueck and McIlwaine, 2002)

1.1.7.2 Medication

1.1.7.2.1 Acetazolamide

Acetazolamide is the drug most commonly used to treat IIH. It inhibits the enzyme carbonic anhydrase, resulting in bicarbonate wasting in the renal tubules and creating a hyperchloraemic metabolic acidosis in addition to a mild diuresis.

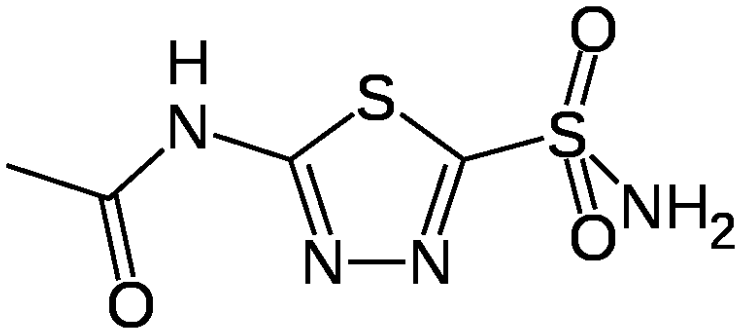


Figure 1.9: Skeletal formula representing the molecular structure of acetazolamide, chemical nomenclature N-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide or $C_4H_6N_4O_3S_2$.

Acetazolamide is used in the treatment of glaucoma due to its effect of lowering intraocular pressure by reducing the production of aqueous humour. It is also used to prevent and treat altitude sickness, via its effect upon ventilation and blood oxygenation. (Leaf and Goldfarb,

2007) The effect of the metabolic acidosis on respiratory function has also lead to its successful use in sleep apnoea syndrome. (White et al., 1982) The mechanism of action in IIH is not fully understood. Early studies in rabbits showed a reduction of CSF production following administration of acetazolamide (Tschirgi et al., 1954) and the first study to demonstrate a similar effect in humans was that of eleven patients by Rubin et al (1966) Subjects ranging in age from 9 to 61 years were studied under conditions of regulated intracranial pressure, during CSF perfusion chemotherapy for CNS tumours. CSF production was calculated from measurements of concentrations of inulin added to the perfusates. Intravenous acetazolamide was found to reduce the rate of CSF production to varying degrees amongst the subjects, but always with a maximum response achieved in the first 90 minutes and a maximum duration of response not exceeding 30 minutes. In a more recent study, Schoeman et al (1994) studied eight children receiving acetazolamide for IIH using continuous lumbar CSF pressure monitoring. Mean baseline pressure was significantly lower after one week of treatment and normalised within six weeks of treatment onset in all cases.

A study in rabbits linked the effect of acetazolamide to the inhibition of carbonic anhydrase in the choroid plexus, where epithelial cells are structurally similar to those lining the renal tubules. McCarthy and Reed (1974) showed that the maximum absolute reduction in CSF flow with intravenous acetazolamide was 50% and that the acetazolamide had no effect upon CSF production until well over 99% of the carbonic anhydrase activity, measured by a changing-pH method, had been inhibited. However, different animal studies have shown that acetazolamide diminishes the rise in CSF bicarbonate when given by direct intraventricular administration but not intravenously, suggesting that its clinical effects are not due to carbonic anhydrase inhibition within the CNS.(Leaf and Goldfarb, 2007)

Acetazolamide is theoretically capable of crossing the blood-brain barrier, but it is likely that only negligible concentrations accumulate when given in normal human doses, particularly via the oral route as is common practice in IIH. Typical oral doses also fail to produce a rise in cerebral blood flow, suggested by some as an alternative mechanism of action. (Huang et al., 1988; Grossmann and Koeberle, 2000)

Acetazolamide belongs to the sulphonamide group of drugs and can be associated with rashes, electrolyte disturbances and nephrocalcinosis. Aplastic anaemia is a rare adverse effect for which some clinicians routinely screen. Patients frequently complain of paraesthesiae (altered sensation or 'pins and needles') as well as parageusia (altered taste), especially with carbonated drinks. The latter, as well as reported side effects of nausea and anorexia, has led to the suggestion that part of the apparent efficacy of acetazolamide can be attributed to reduced oral intake and subsequent weight loss. (Wall, 1995)

Not only is the mechanism of action of acetazolamide unclear, but the magnitude of its clinical effect in IIH, in any, is unproven. No randomised controlled trials of acetazolamide have been undertaken and retrospective studies frequently report its use in combination with other modalities. In an Australian case series, acetazolamide was the primary treatment in 45 (31%) of 144 cases of adult and childhood IIH. (Johnston et al., 1981) Of these 45 cases, it was judged to be effective in 21 (47%), ineffective or partly effective in 22 (49%) and stopped due to complications in two cases (4%). Acetazolamide was the most common treatment in the prospective study by Wall and George, (1991) given to 29 of the 50 patients enrolled. By the end of the study, 11 of these patients were classified as better, 11 as unchanged and 7 as worse when their visual fields were compared.

Johnson et al (1998) studied 15 women with IIH who received a minimum of four weeks treatment with acetazolamide during a 24-week period. Nine of the 15 patients had complete resolution of their papilloedema during the study and a further two, partial improvement. Four patients showed no improvement in their optic disc appearance, despite acetazolamide treatment. All of the patients who improved had lost weight, with a significant correlation between degree of papilloedema resolution and percent weight reduction, but the four subjects with no improvement had lost no weight during the study. The authors concluded that the improvement was due to the weight reduction rather than acetazolamide in this cohort.

Only one small prospective trial involving acetazolamide in IIH has been carried out to date. Celebesoy et al (2007) recruited 40 adults with IIH to an open-label study comparing acetazolamide with topiramate. Alternate allocation, not randomisation, was employed to assign patients to either drug and patients were assessed at three, six and 12 months. No difference was found between the visual field grades in either group at any time point, although a significant improvement was seen overall. The widespread use of acetazolamide has thus developed in the absence of a robust evidence base. It is likely that the low cost, ease of administration and relatively good tolerability as well as a lack of proven alternatives have contributed to its popularity.

Acetazolamide is generally avoided in pregnant patients. The United States Food and Drug Administration (FDA) categorises it in 'Pregnancy Category C, ('animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.') Slight differences exist in the Australian classification, where

Pregnancy Category B3, ('Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed') is applied to acetazolamide. Teratogenic effects have been reported in animals, such as cortical and limb malformations. There are no adequate human studies of its use in pregnancy and a recent review of the literature failed to find any reliable reports of adverse pregnancy outcomes amongst women treated with the drug. (Lee et al., 2005)

1.1.7.2.2 Diuretics

If acetazolamide is poorly tolerated, diuretics such as furosemide are sometimes substituted. A few reports in the literature describe the ability of furosemide to reduce CSF production. In the rabbit studies by McCarthy and Reed (1974) both furosemide and acetazolamide were shown to depress production of CSF for several hours after intravenous administration. Interestingly, for an equal reduction of CSF production, inhibition of carbonic anhydrase activity by acetazolamide was significantly greater than that by furosemide. This suggests that a mechanism other than carbonic anhydrase inhibition is involved in the reduction of CSF formation by furosemide. More recent rabbit experiments showed that maximum CSF flow reduction of 20% was achieved by intravenous furosemide compared to a 40-60% reduction after infusion of acetazolamide. (Vogh and Langham, 1981) In the same study, bumetanide was shown to have no effect on CSF production.

There is very little data in the literature regarding the clinical use of diuretics in IIH. Jefferson and Clark (1976) concluded that 'dehydration therapy alone is sufficient treatment for IIH' following their study of 25 adults treated with hydroflumethiazide, chlorthalidone, oral

glycerol or urea. Striking improvements in papilloedema, improvement in visual acuity and reduction in blind spot size on serial measurements were presented as evidence that dehydrating agents could entirely remove the need for surgery in treating IIH. Two prospective studies from a Danish centre reported the use of chlorthalidone or furosemide in addition to acetazolamide as standard medical therapy for IIH. (Krogsaa et al., 1985; Sorensen et al., 1988) No study has systematically examined the use of diuretics and it seems their main use is as an alternative when acetazolamide is contraindicated.

1.1.7.2.3 Corticosteroids

A beneficial response to corticosteroid treatment in IIH was first reported by Paterson et al. (1961) Rapid improvement in the symptoms and signs of raised intracranial pressure was observed in five of six patients, the response being described as 'not uniform' due to its absence in one patient. Corticosteroids were widely adopted over the following three decades as first line management, chosen in preference to other measures such as repeated lumbar punctures and diuretics or given in addition.

Steroid administration has been shown to be effective in reducing brain swelling and is standard practice in the management of some causes of cerebral oedema. (Rasmussen and Gulati, 1962) Studies have also shown that steroids can reduce CSF production. (Lindvall-Axelsson and Owman, 1990) The effect of steroids on CSF absorption is less clear. One study in dogs showed that four weeks of high dose steroid administration had no effect on infusion tests of resistance to outflow or CSF absorption measured by radionuclide studies. (Johnston et al., 1975) In a study of nine patients treated for 'pseudotumour cerebri' with oral prednisolone, two patients were tested for CSF outflow resistance before and after four

weeks of therapy. In this case, marked reduction in resistance as well as a decrease in resting CSF pressure was observed after treatment, associated with marked resolution of symptoms.

High-dose intravenous methylprednisolone has been suggested as a treatment for florid papilloedema and acute severe visual loss in IIH following an observation by Liu et al (1994) that it led to rapid reversal of visual dysfunction and lasting clinical improvement in three of four patients tested. Patients received tapering oral doses of steroid after five daily infusions, but were also receiving oral acetazolamide. In a larger series, 31 of 37 patients in an initial cohort treated with steroids alone (prednisolone, betamethasone or dexamethasone) had resolution of all symptoms and signs. (Johnston et al., 1981) Seven of the patients had intracranial pressure monitoring which showed a significant reduction after three months, although pressures were still above normal. A later cohort from the same study showed the use of steroids alone to be less effective, leading to clinical improvement in just 11 of 31 patients, one of whom had later recurrence of their disease. Neither of the two studies adhered to rigorous diagnostic criteria for IIH and probably included cases of cerebral venous sinus thrombosis, such that the mechanism of action of corticosteroids as well as the aetiology of the intracranial hypertension was variable. Nine of the 50 patients with IIH in the prospective study by Wall and George (1991) received corticosteroid therapy, five of whom had clinical improvement at the end of the study. The remaining four had a worse outcome, based on visual field and papilloedema grade, such that they were referred for surgical treatment. Some of the patients received acetazolamide in addition to the corticosteroids and the study was not designed or powered to evaluate the effect of intervention.

Concerns over the side effects of steroid treatment have greatly reduced their use. A complication rate of 13% was reported in the series reported by Johnston et al, (1981) with steroid therapy resulting in diabetes mellitus, fluid retention, peptic ulceration, weight gain and psychotic symptoms. Weight gain is a particularly unwelcome long term effect in the typical IIH patient, so corticosteroids are now rarely included as first line management.

1.1.7.2.4 Octreotide

The somatostatin analogue octreotide has been shown to ameliorate headache and improve visual symptoms and papilloedema in three patients with IIH. (Antaraki et al., 1993) In two of these patients, a reduction in CSF pressure was found when measurements pre and post treatment were compared. More recently, a Greek centre recruited 26 patients with IIH to an open label prospective study of daily treatment with subcutaneous octreotide injections for a mean duration of 42 weeks. (Panagopoulos et al., 2007) Significant clinical improvement in headache and papilloedema was observed in 24 of the 26 patients (92%). Median times to improvement of headache and papilloedema were seven and 45 days respectively. Visual disturbances affected 20 of the study patients and resolved by the end of the three year follow up period in 18. The two patients who did not respond to octreotide therapy also failed to improve when treated with acetazolamide plus corticosteroids and went on to receive surgical intervention. CSF pressure measured at lumbar puncture before and one month after treatment showed a significant reduction from 34.4 to 14.7 cm (mean values), $p<0.001$.

No other trials have been performed to assess the role of octreotide in IIH. The study by Panagopoulous et al (2007) was uncontrolled and unblinded, so limited conclusions can be drawn. Octreotide exerts inhibitory effects on the growth hormone / insulin-like growth factor axis (Plewe et al., 1984) and has been used for the treatment of headache associated with acromegaly and pituatory tumours with some success. (Williams et al., 1987) There are also case reports of its use in migraine (Kapicioglu et al., 1997) and cluster headache. (Matharu et al., 2004) Whether the apparent benefit in some IIH patients is due to an analgesic mode of action in addition to an effect on the raised intracranial pressure is unknown.

1.1.7.2.5 Topiramate

The antiepileptic drug topiramate, a sulfamate-substituted monosaccharide, has a complex mode of action with multiple mechanisms including some weak carbonic anhydrase inhibition. Initially licensed for the control of seizures, it has become a recognised migraine treatment and has been used off-licence in a variety of other conditions. A case report in 2002 described improvements in headache and visual symptoms amongst three obese female patients with IIH when topiramate was given, where acetazolamide had been used without success. (Pagan et al., 2002) A later case report showed that papilloedema and headache improved in a 20 year old female when topiramate was introduced to treat recurrent IIH after acetazolamide, CSF drainage and corticosteroids had failed. (Finsterer et al., 2006) A retrospective chart review by Shah et al (2007) identified 17 female IIH patients treated with topiramate between 1997 and 2005 and studied a variety of outcome measures over a mean period of 54 months. Topiramate was used with acetazolamide in three cases,

with furosemide in one and as single drug therapy in the remaining 13 (76%). Symptomatic improvement was reported in some patients and optic disc oedema either improved or stabilised in all patients. There was a significant improvement in mean disc oedema grade ($p=0.033$) but not in the Humphrey automated perimetry mean deviation ($p=0.58$). Seven patients lost weight, but quantities were not provided. Despite the limitations of the study, the authors recommended that topiramate be considered as an adjuvant or second-line agent for the treatment of IIH.

One study has attempted to examine the use of topiramate for IIH in a clinical trial. In the Turkish study by Celebisoy et al (2007) 20 patients received topiramate as an alternative to acetazolamide by a random-allocation design. Although a treatment effect was not found, 'prominent relief' of headache was reported after a mean treatment period of 3.75 months (mean 3.3 months in patients receiving acetazolamide). Weight loss was observed amongst patients in the topiramate arm over the 12 month study period (mean 9.75kg), significantly more than that in the acetazolamide arm ($p<0.001$). Other side effects reported were distal paraesthesiae and concentration difficulties, although no patient discontinued the drug.

Some centres now routinely consider topiramate as an IIH treatment option. Where headache is a prominent symptom, the known migraine prophylaxis effect may be beneficial, especially where there are migranous characteristics to the IIH headache or the two conditions co-exist. Topiramate has also shown benefits in a variety of other headache disorders. (Silberstein et al., 2006) Headache is the most common and disabling symptom of IIH and successful management often needs to include adequate analgesia. The side effect of weight loss may also be an advantage for obese patients.

1.1.7.2 Surgery

Some patients require surgical intervention to control their symptoms or prevent deterioration of their visual function. Surgical treatment needs to be considered from the outset for patients presenting with visual loss and at any time when there is deterioration in visual function. (Lueck and McIlwaine, 2002) Some authors argue that the decision to operate rests entirely on the quantitative visual field status. (Corbett and Thompson, 1989) Surgery may also be appropriate where close monitoring and effective medical treatment of the patient is not feasible, or if there is intractable headache.

1.1.7.2.1 Subtemporal decompression

Introduced in the late 19th century, the technique of craniectomy and opening the dura over the inferolateral surface of the temporal lobe to decompress the brain was for many years standard surgical practice for resistant cases of intracranial hypertension. The procedure can be unilateral or bilateral. The main complications are epilepsy, meningitis and focal neurological deficit as well as the usual complications of major surgery, including death and venous thromboembolism. (Johnston et al., 2007)

The outcome after subtemporal decompression for IIH has not been formally studied and early reports indicated wide variability in its effects on symptoms and CSF pressure. (Davidoff, 1956; Jacobson and Shapiro, 1964) In the Glasgow series by Johnston et al, (1981) subtemporal decompression was performed in 43 patients, in five cases as the initial treatment. In the majority, it was used after serial lumbar punctures had failed to control the intracranial hypertension. 30 (70%) of the 43 patients had resolution of all symptoms and signs within six months of the procedure. The remaining 13 patients required further

treatment after the surgery and five had worsening of their vision post-operatively. Epilepsy complicated 12 of the 43 cases and two patients had late recurrence of their IIH, two and 14 years later.

More recently, Kessler et al (1998) conducted a retrospective review of eight patients treated with 'liberal' decompression via 6-8cm temporal craniectomies. All cases were female and had progressive worsening of visual function despite diuretics and serial lumbar punctures. All patients had prompt resolution of their papilloedema within one month of surgery, but only three remained symptom free over the mean follow-up period of 21 years. In addition, five patients needed CSF diversion procedures less than two months after the original surgery, due to persistence of headaches and tense bulging at the craniectomy site. The authors claim that subtemporal decompression should be regarded as a 'first-line therapeutic option in any patient who fails medical treatment'.

The role of subtemporal decompression in IIH is now limited and has largely been replaced with less radical procedures. It may be an option for a small number of patients when such procedures fail. Where it is used, bilateral craniectomies with specific techniques of dural splitting to protect the cortical surface are recommended. (Johnston et al., 2007)

1.1.7.2.2 CSF Diversion Procedures

CSF diversion procedures involve diverting the CSF from the lumbar subarachnoid space to the peritoneal cavity (lumbo-peritoneal or LP shunt) or from a lateral ventricle to the peritoneal cavity (ventriculo-peritoneal or VP shunt), the right atrium (ventriculo-atrial, VAT shunt) or the pleural space. CSF flow occurs from high to low pressure, through a catheter with a valve device to prevent reversal of flow. CSF diversion procedures have a significant

failure rate which can require revisional surgery, as well as a high frequency of complications, including over drainage and low pressure headaches, infections, obstruction and general operative complications. (Rosenberg et al., 1993) Less commonly, subdural haemorrhages, radiculopathies, tonsilar herniation and syringomyelia have been reported. (Lueck and McIlwaine, 2002)

Generally, ventricular shunts are more straightforward to insert, although LP shunts may be technically easier in the presence of smaller ventricles. LP shunts can be more difficult to anchor however, which may lead to catheter dislocation. For some patients, drainage of the ventricular system or lumbar subarachnoid space is impossible, due to such anatomical factors as small ventricles, spinal deformity and scarring of the lumbar thecal space or impractical, due to failure of previous LP or VP shunts. Lee et al (2004) published a case series of five patients with 'pseudotumour cerebri' who had catheters placed directly into the cisterna magna (cerebromedullary cistern). The distal shunts drained into the pleural space or via the internal jugular vein into the right atrium. Intracranial telemetric pressure recordings demonstrated that intracranial pressure was lowered, but two of the patients required shunt removal for complications. In the three patients who kept their shunts, there was some improvement in headache although all continued to require additional pain management. The high complication rate probably limits the use of this type of shunt to patients lacking a more suitable drainage site.

Complications are common and limit the effectiveness of all shunts. A review of 37 LP and nine VP shunts in 73 patients from six US institutions found that only 14 patients (19%) remained symptom free after a single procedure. (Rosenberg et al., 1993) In total, 64% of all shunts in the study needed replacement within six months. After shunt failure (55%), low-

pressure headaches were shown to be the most common adverse events, affecting 21%. According to the author, whichever type of shunt is chosen, the patient can expect an average of 2.2 surgical procedures and a mean time to shunt failure of around 9 months.

There is some evidence from small studies that revision rates may be lower amongst VP shunts. Bynke and colleagues (2004) compared two published series of patients treated with LP shunts to their own cohort of 17 patients who received VP shunts. Annual revision rates, but not the proportion of patients requiring revision, were lower in the VP group. In the same year, McGirt et al (2004) published the findings of a review spanning 30 years in a single US centre. 42 patients underwent 115 procedures between 1973 and 2003, 79 LP shunts and 36 VP or VAT shunts. The risk of shunt obstruction was three times higher amongst the LP shunts, where there was a 2.5-fold increase in risk of shunt revision. Other complications, including over-drainage, distal catheter migration and shunt infection were similar between the groups. Recurrence of headache despite a functioning shunt was also common, occurring in 67% of patients within 36 months. Patients without papilloedema and those with symptom duration of longer than 2 years were shown to have a significantly higher risk of headache recurrence.

The complication rates for all CSF diversion procedures are substantial and may appear unacceptably high to the patient. Nevertheless, carried out by an experienced neurosurgeon, such operations can be sight-saving and have been shown to be effective to varying degrees on all the clinical manifestations of IIH. Techniques have been developed which may improve the effective placement of ventricular shunts, such as endoscopy or stereotactic imaging. These remain to be formally evaluated in IIH and further study of CSF

diversion procedures as a whole are needed, to improve what remains a cornerstone of IIH management.

1.1.7.2.2 Optic Nerve Sheath Fenestration

In this procedure, the optic nerve is decompressed, via a fenestration or 'window' in the surrounding sheath. An incision is made in the orbit via a medial or lateral approach, and the optic nerve immediately behind the globe approached. (Figure 1.10) An incision is made in the dura mater of the nerve sheath up to a maximum of 1cm in length, or occasionally multiple smaller openings are created. (Keltner, 1988) A transnasal endoscopic approach has also been described in a case report of one patient. (Gupta et al., 2003) Unilateral procedures are usually carried out, with the second eye being operated on at a later date if worsening vision occurs, although bilateral optic nerve sheath fenestrations (ONSF) are sometimes undertaken.

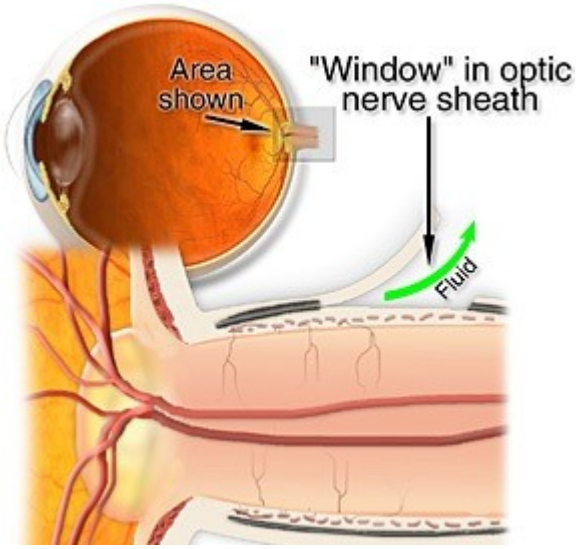


Figure 1.10: Cross-section of optic nerve showing site of optic nerve sheath fenestration

The exact mechanism of action of ONSF is uncertain. One theory is that the effect is due to the formation of a chronic fistula, such that the egress of CSF is maintained and the CSF pressure on the nerve sustained. (Keltner, 1988) An alternative explanation is that there is localised scarring of the meninges, such that transmission of the high CSF pressure to the optic nerve head is prevented. The situation is further complicated by the observation that unilateral ONSF procedures can lead not only to resolution of optic nerve swelling on the side of the surgery, but also to improvement of contralateral disc swelling and even headaches, suggesting an effect beyond localised lowering of pressure.(Berman and Wirtschafter, 1992; Acheson, 2004)

To an experienced ophthalmic surgeon, ONSF is a relatively minor procedure and, unlike shunts, involves no insertion of foreign bodies. (Lueck and McIlwaine, 2002) Complications are usually transient and benign. Diplopia, oculomotor disorders, anisocoria (inequality of pupil diameter) and dellen (localized reduction of corneal thickness) are the most prevalent adverse events and repeat procedures are occasionally required. (Keltner, 1988; Banta and Farris, 2000)

Resolution of papilloedema following ONSF is often, but not always, associated with improvements in visual acuity and fields. In a study of 86 patients (158 eyes) treated with ONSF, visual acuity and visual fields improved or remained stable in 94% and 88% respectively. (Banta and Farris, 2000) A more recent, smaller study found significant improvement in visual field mean deviation scores following ONSF ($p=0.03$) and self-limiting complications in just five of 32 patients. (Chandrasekaran et al., 2006) A UK 5-year audit by Knapp and Sampath (2005) reported that ten (77%) of 13 patients were able to discontinue medical therapy following ONSF. Visual fields were improved in 18 of 27 eyes, unchanged in

two and worse despite surgery in four. Acuity improved in only four patients and was unchanged in the remainder.

Visual function may deteriorate many years after ONSF. Even after initially successful operations it may be necessary to proceed to CSF diversion, to halt progressive visual loss or treat intractable headaches. (Spoor et al., 1994; Banta and Farris, 2000) No prospective trial has ever compared ONSF and CSF diversion. In clinical practice, the choice between ONSF and CSF diversion is often made on the basis of local preference and available expertise as well as the balance between headache and visual symptoms as predominant features in the individual case. (Binder et al., 2004)

1.1.7.2.4 Endovascular stenting

The inclusion of endoluminal venous sinus stenting as a surgical option for IIH is controversial, but the procedure is worthy of mention due to its recent popularity in specific centres and patient groups. If the evidence for the existence of intracranial venous outlet obstruction in 'true' cases of IIH is accepted, it is understandable that attempts to evaluate the effects of surgically relieving the obstruction have been undertaken.

Isolated case reports in the literature appeared to show that placement of an endoluminal stent could result in clinical improvement in IIH. These were followed in 2008 by a study undertaken to assess the clinical and radiological outcomes amongst ten adult patients with IIH treated consecutively with endovascular venous stenting. (Donnet et al., 2008) All patients had headache, papilloedema and other clinical features refractory to treatment with acetazolamide as well as stenoses demonstrated on three-dimensional MR venography.

Papilloedema and tinnitus resolved in all subjects, headache in six (60%). Three months post treatment, CSF pressure was below 19cm in all patients (mean pre-treatment 40.2cm.)

The striking clinical improvements and the lack of adverse events reported make the technique seem attractive as an alternative management strategy. Further investigation to assess the importance of venous sinus pathology in the aetiology of IIH as well as evaluation of the safety and efficacy of the stenting procedure is required, before clear recommendations can be made.

1.1.7.3 Weight Reduction

It is widely believed that weight reduction improves the course of IIH amongst overweight individuals. The striking and robust association between IIH and obesity, as well as observations since the earliest descriptions of the condition that weight loss accompanied clinical improvements, has led to advice about weight reduction being standard clinical practice. Only a few studies have attempted to assess the effect formally.

In 1974, nine patients were reported whose papilloedema resolved after a mean weight loss of 34 kilograms, through a low calorie adaptation of a rice diet. (Newborg, 1974) A more recent study of 58 patients showed significantly lower grades of papilloedema amongst those who lost at least 2.5 kilograms during any 3-month period, but no significant differences in their visual fields or acuities. (Kupersmith et al., 1998b) A positive relationship between weight reduction and improvement of optic nerve swelling was also demonstrated by Johnson et al (1998) in a retrospective review of 15 female IIH patients. The average weight loss in six patients who had marked resolution of their papilloedema was 6.2% and, whilst the study included patients who were also taking acetazolamide, a significant

correlation was found between percentage weight reduction and change in papilloedema grade.

Surgically-induced weight loss has also led to case reports of improvements in IIH. Loss of 36.9 kilograms due to a gastric exclusion procedure was associated with a reduction in the CSF pressure, disappearance of papilloedema and near-normalisation of visual fields in one obese patient. (Amaral et al., 1987) Sugerman et al (1999) studied 24 severely obese female IIH patients treated surgically with gastric bypass in 23 and gastric banding in one. Within four months of surgery, papilloedema and cranial nerve dysfunction had resolved in all women; headache and tinnitus improved in all but one patient. Over time, weight regain in two patients was associated with a recurrence of symptoms. Normalisation of elevated dural venous sinus pressures has also been shown to accompany the successful treatment of IIH with weight-reduction surgery. (Nadkarni et al., 2004)

The first prospective study to formally evaluate the effect of weight loss in IIH was reported by Sinclair et al. (2009). Symptoms, headache severity and papilloedema were shown to improve significantly amongst 25 adult females with longstanding IIH who lost an average of 15.2kg body weight on a low-calorie, supervised, total meal replacement diet over three months. In addition, the mean intracranial pressure, as measured by serial lumbar punctures, was shown to fall significantly following the intervention. Whilst visual acuity and Humphrey visual field mean deviation scores showed no change throughout the study, objective evidence of improvement following weight loss of optic nerve swelling, using ultrasonographic measurement, was provided.

Despite growing evidence, further research is required to quantify the optimum amount, timing, and methods of weight loss in IIH management. There appears to be a subgroup of

IIH patients for whom weight loss may be the only action required to bring about resolution of their clinical symptoms. There is certainly sufficient data to support the routine inclusion of dietary and other weight-reduction advice into standard IIH management strategies.

1.1.7.4 Monitoring

There is no consensus about the most effective way to monitor patients with IIH, or which clinical assessments most reliably identify those patients at greatest risk of visual loss. If the arguments against repeated lumbar punctures as a treatment for IIH are upheld, regular measurement of the intracranial pressure to monitor the condition is similarly not an option. Furthermore, lumbar punctures can fail to accurately measure fluctuating CSF pressure and may provide 'isolated fragments of information that cannot be depended on for therapeutic decision-making'. (Corbett and Thompson, 1989)

Formal perimetry seems to be the most precise method of identifying visual loss and has been shown to exhibit statistically greater sensitivity in comparisons with Snellen acuity and contrast sensitivity. (Rowe and Sarkies, 1998) This is explored and discussed in chapter 3.

1.1.7.5 Outcome

1.1.7.5.1 Visual Loss

For the majority of patients, IIH lives up to its old name as a benign condition, without impairment of vision in the long term. However, there are a small but significant number of patients for whom the condition follows a more aggressive course. Blindness does occur and several studies have demonstrated sustained loss of vision in IIH, as summarised in table 1.5.

Table 1.5: Published reports of visual loss as an outcome of IIH

Year	*Study type*	*Author*	*Nº. of patients*	*Nº. with visual loss (%)*	*Comment*
1974	Retrospective	Boddie et al	34	4 (8)	Three patients had visual loss at presentation
1980	Retrospective	Rush	63	7 (11)	Visual acuity worse than 6/9 at last visit
1982	Retrospective	Corbett et al	57	14 (25)	24 eyes in 14 patients blind or profoundly visually impaired
1984	Retrospective	Orcutt et al	68	21 (31)	5 eyes in 4 patients severe visual loss
1988	Prospective	Sorensen et al	24	1 (4)	Plus chronic papilloedema in 42%
1991	Prospective	Wall et al	50	5 (10)	Two patients blind in both eyes, three blind in one eye
1993	Prospective	Radhakrishnan et al	81	16 (20)	Moderate to severe loss. Mild loss in a further 21%
1998	Prospective	Rowe et al	35	6 (17)	Three patients had visual loss + optic atrophy at presentation

In an early, retrospective review of 34 patients, four (8%) had sustained visual impairment, although three of these had severe visual symptoms and signs at presentation. (Boddie et al., 1974) Rush (1980) described seven patients with final Snellen visual acuity worse than

6/9 from a cohort of 63 observed over a seventeen period, none of whom improved despite treatment. In the study by Corbett et al (1982) spanning five to 41 years of observation, half of the eyes studied in 57 patients had no loss of visual field or acuity at a follow up assessment, but 24 eyes in 14 patients were blind or profoundly visually impaired. In 11 of these patients, loss of sight occurred gradually or in a stepwise fashion over months or years, but in eight, the visual loss at presentation was as severe as it would ever be. The rate of loss of vision was variable and for many patients, symptoms were minimal and the loss undetected until severe. Orcott et al (1984) reported visual dysfunction (described as reduction in visual field and / or acuity) in 21 (31%) of 68 patients and some definite loss of vision in 49% of all eyes, of which 6% was severe.

Amongst 24 patients studied prospectively in Denmark, only one had optic atrophy and severe visual impairment after a mean observation of 49 months, yet ten patients (42%) developed chronic changes of the optic disc. (Sorensen et al., 1988) In the study by Wall and George, (1991) two of 50 patients became blind in both eyes and three developed blindness in at least one eye. In the Libyan population survey, 20% of patients had moderate to severe loss of vision at follow up, with only 58.6% of patients having entirely normal visual field status. (Radhakrishnan et al., 1993) In a more recent, prospective study involving 35 patients, a poor outcome in terms of visual fields was documented in 17%, but three of these patients presented with visual loss and had evidence of optic atrophy on examination. (Rowe and Sarkies, 1998)

An attempt to describe the incidence and characteristics of acute and rapidly progressive visual loss in a series of 16 patients with ‘fulminant’ IIH was published in 2007. (Thambisetty et al., 2007) Amongst 572 patients from two centres over a ten year period, 16 (2.8%) were

identified who fulfilled the criteria of acute onset of signs and symptoms and visual loss occurring within 4 weeks of presentation or rapid worsening of visual loss over a few days. Visual loss was very rapidly progressive in all patients; the time between the patients' first symptom and their worst visual loss ranged from 7 to 28 days (mean 16.1.) All of the patients received surgery following their initial medical management (ONSF in 5, LP shunt in 9, VP shunt in 2 patients.) Despite this, visual field abnormalities persisted in all patients and eight (50%) remained legally blind.

Accurate information regarding the natural history of IIH is difficult to obtain and early studies may be inaccurate if strict adherence to modern diagnostic criteria was not observed. However, a conservative estimate based on available data is that 10% of patients exhibit lasting and clinically relevant visual loss. Aggressive surgical intervention may be required in a small group of patients and the need for watchful monitoring is clearly apparent, especially since patients may be asymptomatic until visual disaster has already occurred.

1.1.7.5.2 Risk Factors for poor outcome

Attempts have been made to identify clinical and demographic features that may predict the course of IIH. Several studies have explored the characteristics of patients showing worse visual outcome. Corbett et al (1982) found that visual deterioration was not predicted by the presenting symptoms, with the exception of frank visual loss at onset. A statistically significant association was found, however, between visual loss and systemic hypertension, since 61% of patients with persistently elevated blood pressure had marked unilateral or bilateral visual impairment when re-examined. Poor outcome in the study by Orcutt et al

(1984) did not correlate with gender, symptoms, chronicity of papilloedema, high CSF pressure or excess body weight. Patients with a known cause of intracranial hypertension were also included in this study, but the presence or absence of a known cause was also not associated with a particular outcome. Similarly, Radhakrishnan et al (1993) found no correlations with visual outcome amongst age at diagnosis, body weight, duration of symptoms, oral contraceptive use, steroid treatment, nor CSF opening pressure. Amongst the 16 cases of 'fulminant' IIH described by Thambisetty et al, (2007) four had controlled systemic hypertension but the group appeared to have no remarkable clinical characteristics to explain their poor outcome.

Gender has been shown by some studies to have an effect on IIH. Kesler et al (2001) observed that 78% of women but only 25% of men were overweight in a retrospective review of 141 patients and that diagnosis of IIH appeared to be made later amongst male patients. Digre and Corbett (1988) compared 29 men with 'pseudotumour cerebri' to age matched female patients and concluded surgical intervention may be required more frequently to prevent visual loss in men. Further evidence of a worse prognosis amongst men was provided by a retrospective review of 721 consecutive IIH patients. (Bruce et al., 2009) Men (66) had significantly worse visual acuities and visual fields at initial and final evaluations than 655 women, with a relative risk of severe visual loss, defined by the US criteria for legal blindness, of 2.1 ($p=0.002$.) Male sex remained an independent factor for severe visual loss in at least one eye when adjusted for age and diagnosis of sleep apnoea.

The effect of race on outcome was examined by the same author in a retrospective chart review. (Bruce et al., 2008) Black patients (197) were found to have higher CSF opening pressure, worse LogMAR acuities, worse visual field grades and higher degrees of

papilloedema than 253 non black patients with IIH. The relative risk of severe visual loss for black patients compared with non-black patients was 3.5 ($p < 0.001$) in at least one eye and 4.8 ($p < 0.001$) in both eyes. Logistic regression analysis identified race, anaemia, BMI and male gender as independent risk factors for severe visual loss.

The apparently beneficial effect of weight reduction on the clinical course of IIH supports the finding by some studies that body weight affects outcome. Of the many variables examined by Wall and George, (1991) only weight gain over the year preceding IIH diagnosis was significantly associated with visual deterioration as measured by perimetry grade. None of the patients without weight loss in Johnson's study had improvement in their papilloedema. (Johnson et al., 1998) Other studies have failed to show a clear association between body mass and outcome.(Corbett et al., 1982; Orcutt et al., 1984; Rowe and Sarkies, 1998)

No study has specifically compared IIH outcome between children and adults or formally evaluated the effect of age on final visual function. Small reports have suggested that poor visual outcome in children may result, at least in part, from difficulties in communication of symptoms and clinical assessment. (Cinciripini et al., 1999; Rowe and Noonan, 2002; Scott et al., 1997) A retrospective case series of 96 patients found that pubertal patients had a less favourable outcome than prepubertal, teenage and adult patients. (Stiebel-Kalish et al., 2006) Puberty was identified as the sole predictor of poor outcome, the definition of which included permanent visual field constriction and evidence of optic neuropathy. Logistic regression analysis of the data suggests that a less favourable outcome is in IIH associated with a 'critical period' around puberty. A secondary observation from the study was that severe, high grade papilloedema at presentation appeared to correlate with poor outcome.

Several studies have associated the severity of papilloedema with poor outcome. Patients with high grade or atrophic papilloedema as well as haemorrhages near the disc had worse visual outcome in the study by Orcutt et al. (1984) The presence of additional features at fundoscopy, such as haemorrhage and exudates, have been found to accompany significant central field losses.(Friedman and Jacobson, 2002) Wall and White (1998) studied a series of patients with asymmetric papilloedema to determine whether visual loss was related to the degree of disc swelling. Nine patients judged to have interocular papilloedema difference of two or more Frisen grades underwent detailed prospective assessment of their visual function. Vision was worse in the eyes with the more severe disc swelling on all measures, including three different visual field assessments, visual acuity, colour vision and contrast sensitivity. Interestingly, the prospective study of 50 patients by the same author found that the severity of visual loss could not be predicted from the severity of the papilloedema. (Wall and George, 1991) Other studies have failed to demonstrate a clear relationship between papilloedema and visual outcome, including that of Corbett et al. (1982) Visual loss was not statistically related to the degree of papilloedema in the study by Rush, (1980) nor to the presence of visual obscurations and duration of symptoms. In some cases, the development of optic atrophy and its impact on the appearance of the disc may explain the apparently conflicting findings. In addition, the assessment of papilloedema has been largely subjective to date, as discussed in chapter 4.

1.1.7.5.3 Recurrence

IIH can reoccur months to years after the original episode has resolved. Five of the patients in the study by Corbett et al (1982) had recurrent disease, occurring four months to nine

years after the initial attack. No particular risks to vision were identified amongst the recurrent cases. The investigation by Kesler et al (2004b) of 54 patients with IIH over a mean period of six years, found that only 33 (61%) had a single episode. Seven patients had two episodes, ten had three, three patients had four episodes and one patient had a total of seven. None of the relapses occurred in patients taking acetazolamide and no recurrences were observed beyond 72 months, although this reflected the design of the study.

Researchers in Iowa reviewed 410 adult patients to evaluate recurrence in IIH, defined as return of symptoms after resolution and return of previously resolved papilloedema after no medication had been given for at least six months. (Shah et al., 2008) Twenty patients were identified who met the inclusion criteria and had been observed over a minimum of ten years. A stable course without recurrence was reported in 11 patients. In six patients, there was a delayed worsening of clinical features following an initially stable course, after a mean period of 72 months. Three patients had 'true' recurrence of disease, after 12, 31 and 78 months respectively.

Crude IIH recurrence rates from the three studies are calculated as 8% (Corbett et al., 1982) 38% (Kesler et al., 2004b) and 15%. (Shah et al., 2008) It is already clear from the literature that many patients will require monitoring over long periods and this is reflected in modern clinical practice. Well-designed, prospective, longitudinal studies are required to more accurately predict rates of recurrence as well as to identify predisposing factors for relapses in IIH or for disease that worsens after a period of apparent stability.

1.2 Pathogenesis

1.2.1 Mechanisms of raised intracranial pressure

The pathophysiology underlying the raised intracranial pressure in IIH is unclear. Hypotheses have developed around the main determinants of CSF pressure: the rate of CSF production, the compliance of the CSF space and the resistance to the egress of CSF. (Donaldson, 1981)

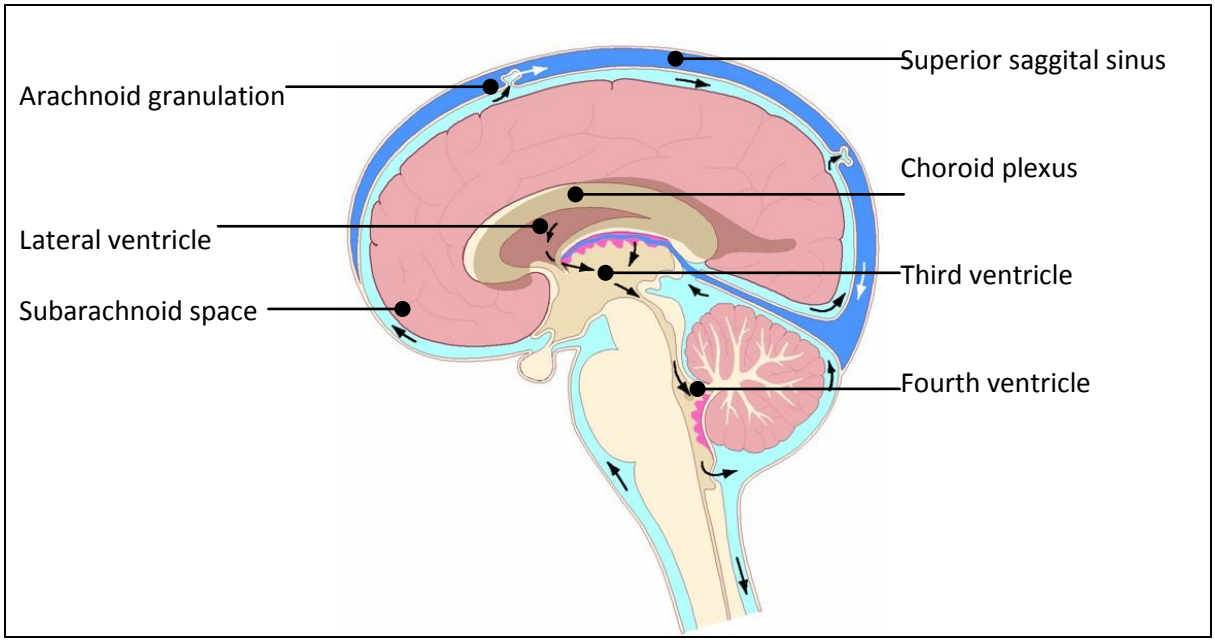


Figure 1.11: Diagrammatic representation of the circulation of CSF in the brain (midsagittal section). Arrows represent direction of CSF flow.

1.2.1.1 Excessive CSF production

CSF is produced by ependymal cells, predominantly in the choroid plexus, a rich network of blood vessels in the ventricles. In humans, the total volume is approximately 140ml. (Speake et al., 2001) The estimated rate of production in humans is 0.37 ml per minute or approximately 500 ml in 24 hours, the whole CSF volume being renewed every 6 to 8 hours.

(Wright, 1978, Wall et al., 2001) CSF circulates from the choroid plexus through the interventricular foramina (foramen of Monro) into the third ventricle, and then through the cerebral aqueduct (aqueduct of Sylvius) into the fourth ventricle, where it exits through two lateral apertures (foramina of Luschka) and one median aperture (foramen of Magendie). It then flows through the cerebellomedullary cistern down the spinal cord and over the cerebral hemispheres. This is shown in figure 1.11.

Early attempts to determine the cause of the raised pressure in IIH suggested that CSF hypersecretion may occur. (Quincke, 1893) The technique of isotope cisternography, in which technetium labelled serum albumin is infused via lumbar catheter, permitted calculation of the estimated CSF production rate and demonstrated the converse, that levels in IIH were even lower than previously quoted normal rates. (Johnston and Paterson, 1974) More recent studies have confirmed the lack of significant differences in the production rate between IIH patients and controls. (Malm et al., 1992) The only condition in which excessive secretion of CSF is known to occur, the uncommon tumour choroid plexus papilloma of childhood, does not give rise to a similar clinical picture to IIH. (Walker, 2001) There is thus little to support the concept of CSF hypersecretion in IIH and it is now largely excluded as a possible cause of the condition.

1.2.1.2 Brain Water Content

Considerable research has failed to show convincing evidence of diffuse brain oedema in IIH. Early histological studies suggestive of intracellular and interstitial oedema in ten patients with IIH were reported by Sahs and Joynt. (1956) The samples were obtained at the time of subcortical decompression procedures and artefactual changes may have been present. The

slides have been re-examined and repeated without confirmation of the initial claims. (Wall et al., 1995)

Imaging studies have also led little support to the theory of increased brain water. MRI studies have tentatively suggested diffuse, mild oedema when heavy T2-weighted and balanced pulse sequences were used. (Moser et al., 1988) Bastin et al (2003) used MRI to measure proton longitudinal relaxation time and mean water diffusivity at various brain regions of ten patients with IIH and ten controls. No significant differences were seen in either parameter, from any region. Bickaci et al (2006) used T1, T2 and fluid retention inversion recovery (FLAIR) MRI sequences as well as three-dimensional time-of-flight to study 16 patients with IIH and 16 controls matched for age, sex and weight. No abnormalities indicative of oedema were seen in any of the various gray matter regions examined.

Accepting the conflicting results of studies, there is little to support a theory of brain oedema in IIH. Cerebral oedema of sufficient severity to increase the intracranial pressure seems incompatible with the degree of preservation of neurological function as well as the generally benign clinical course seen in IIH.

1.2.1.3 Reduced CSF absorption

A more popular hypothesis is that IIH is a syndrome of reduced CSF absorption. The circulating CSF is returned to the systemic circulation via the dural venous sinuses. Studies supporting the arachnoid villi and granulations as the primary absorption sites date back over many years. (Weed, 1914; Pollay and Welch, 1962) Animal studies show that extracranial lymphatics provide an alternative pathway, via transport through the cribriform

plate into the nasal mucosa. (Boulton et al., 1996; Sinclair et al., 2002) An early study used the intrathecal saline infusion test (ITSIT) to show an apparent resistance to drainage of CSF in four out of five patients diagnosed as having pseudotumour cerebri. (Martins, 1973) Johnston and Paterson (1974) published similar work using isotope cisternography to demonstrate a marked delay in CSF circulation, with hold up of technetium isotope in the subarachnoid space. Altered patterns of CSF clearance were reported using similar methods amongst six of seven obese IIH patients by Orefice et al. (1992) Sorensen et al (1986a) used lumbo-lumbar perfusion methods to measure conductance to CSF flow, the reciprocal of resistance; all 11 patients in their study had values below normal. Abnormally low conductance was also shown by Gjerris et al (1985) using this method in all of 14 patients with the diagnosis of benign intracranial hypertension.

In 1992, Malm et al (1992) claimed to have identified two possible mechanisms of the raised CSF pressure in IIH. The following highly significant differences in 13 patients compared to 45 controls were reported: elevated CSF lumbar pressure, reduced conductance of CSF outflow pathways and increased pressure difference across CSF outflow pathways. Amongst those patients whose outflow conductance was very low, a dysfunction of the arachnoid villi was proposed as the cause of the increased hydrostatic pressure necessary to sustain the bulk flow of CSF. In a second group of patients, however, the outflow conductance was normal or only slightly reduced, but high pressures were recorded in the sagittal venous sinuses. The role of cerebral venous sinus pressure in the pathophysiology of IIH is discussed below.

Whatever the mechanism is of the raised CSF pressure, it must account for the lack of ventricular dilatation seen in IIH. If the more likely hypothesis is accepted, that CSF absorption is impaired, it would suggest that there is an increase in the total CSF volume.

This is supported to some extent by the positive clinical response seen in IIH to reduction of the CSF volume, by lumbar puncture or other methods. Measurement of CSF volume is not easily performed and attempts using MRI techniques have been inconclusive. (Condon et al., 1986) The co-occurrence of small or normal-sized ventricles and increased CSF volume would also need explanation. Since in IIH it is assumed no structural blockage exists, ventricular dilatation would only occur once the CSF volume exceeded that which could be accommodated by the freely patent subarachnoid space. It has been suggested that, in IIH, a new equilibrium is reached, in which the system controlling CSF absorption is 'reset' with the elevated intracranial pressure and CSF volume. (Johnston and Paterson, 1974) Levine et al (2000) conducted a comprehensive literature review and presented a detailed mathematical study to explore this further. They were able to demonstrate that small, normal sized or slightly enlarged ventricles can result from increasing CSF pressure uniformly in the ventricles and the subarachnoid space and that the model was consistent with the hypothesis that IIH is caused by abnormal CSF absorption into the bloodstream.

1.2.1.4 Increased cerebral venous pressure

Whether the raised CSF pressure is the primary problem in IIH or the consequence of high pressure in the cerebral venous sinuses, due either to anatomical narrowing or generalised venous hypertension, is widely debated. In patients with proven venous sinus thrombosis (Figure 1.12), the high intracranial pressure that occurs is relieved by drainage or diversion of CSF, although it is uncertain precisely how this happens. (Biousse et al., 1999) Venography shows narrowing of the cerebral venous sinuses leading to functional outflow obstruction in many cases of IIH, in the absence of occlusion by thrombus. In one prospective, blinded MRV

study, substantial, bilateral sinovenous stenoses were seen in 27 of 29 IIH cases, leading the authors to conclude that the dural venous sinuses are anatomically different in this condition. (Farb et al., 2003) Raised pressure, in the absence of thrombosis, within the superior sagittal and transverse sinuses, has been demonstrated by others. (King et al., 1995) Whether such findings are due to high pressure in the CSF or the actual cause of the intracranial hypertension is not known, but there is evidence to support both explanations.

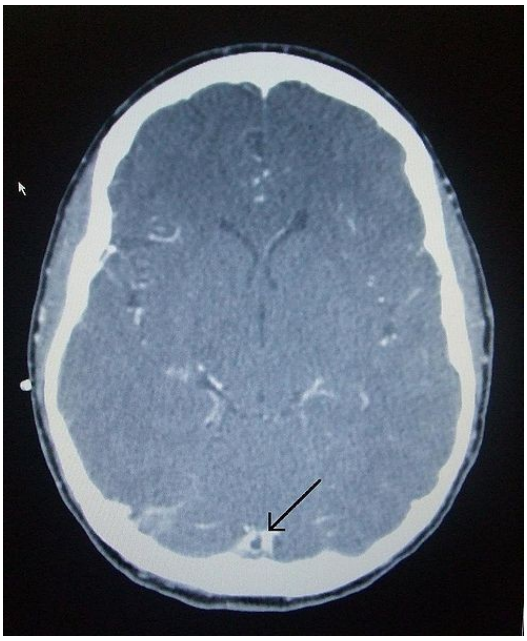


Figure 1.12: CT Venogram showing filling defect in the sagittal sinus (arrow)

The hypothesis of apparent venous stenosis as a secondary effect assumes that the venous compartment will 'give way' to that of the expanding CSF, and that either the vessel walls are externally compressed or that partial obstruction of the lumen occurs, due to enlarged arachnoid granulations. Both types of filling defect were observed in the MRV study by Farb et al. (2003) There have been reports of stenotic lesions in the lateral sinuses resolving after CSF diversion procedures (Higgins and Pickard, 2004) and a demonstration by King et al (2002) of a drop in the measured transverse sinus pressures of eight IIH patients, following

direct removal of CSF by cervical puncture. In the latter study, the largest falls in venous pressure were seen in patients with the highest intracranial pressures, although not all the patients had elevated venous sinus pressure. The results appeared to suggest that obstruction to venous outflow, at the level of the transverse sinus, in IIH is due to high intracranial pressure and is reversed by lowering this pressure. Even if the theory of direct compression of the veins by intracranial pressure is accepted, exactly what expands, or pressurizes, the CSF remains unclear.

The findings of many other studies lend support to the opposing argument: that the venous stenoses are the primary lesion in IIH. Higgins et al (2003) performed dilatation and stenting of the lateral venous sinuses of 12 patients with refractory IIH who were found to have high venous sinus pressures at manometry. Five patients became asymptomatic from their IIH and a further two showed some clinical improvement, although the remainder were unchanged and there was no consistent relationship between the amount of pressure reduction and symptom relief. Karahalios et al (1996) also found high pressure with normal anatomy in the venous sinuses of five patients with IIH, as well as showing that the right atrial pressures were increased, leading them to suggest that right-sided heart failure underlies a 'universal mechanism' of elevated venous pressure in the condition. Sugerman et al (1997) claimed that raised intracranial pressure is a direct result of intra-abdominal pressure, via elevation of the diaphragm, raised pleural pressure, impeded cerebral venous return, and consequently sustained elevation of the venous pressure. However, clinical evidence of right heart failure is usually lacking amongst patients with IIH.

Nevertheless, the possibility of some shared pathophysiological mechanism in IIH and venous sinus disease remains enticing. Unrecognised, non-occlusive thrombus lining the

dural vessels has been suggested as a possible mechanism for the impairment of cerebrospinal fluid absorption leading to IIH. (Sussman et al., 1997) In addition, some authors believe there may be an underlying thrombophilia in IIH patients who have cerebral venous outflow obstruction without demonstrable thrombosis. The familial thrombophilic states are known to predispose to the formation of venous thrombosis, but it is possible that IIH has an independent connection. Backhouse et al (1998) reported two cases of Factor V Leiden mutation in association with IIH and a single case of essential thrombocythaemia in combination with IIH, in a female patient who had venous sinus obstruction excluded by angiography, has been reported. (Esack et al., 1989) A further case of IIH in association with raised serum anticardiolipin antibodies and strong lupus anticoagulant activity, but no evidence of cerebral sinus thrombosis is reported. (Orefice et al., 1995) Dunkley and Johnston (2004) discovered thrombophilic defects in 17 out of 25 patients with a diagnosis of pseudotumour cerebri, only four of whom were found to have frank cerebral venous thrombosis. Sussman et al (1997) studied the strength of association between risk factors for thrombosis and IIH in more detail. Amongst their findings was an incidence of antiphospholipid antibody of 31% in 29 patients with IIH, compared to 6% in 16 healthy control subjects and 17% in 18 patients with other neurological disorders recruited as a second control group, although the statistical analysis of these results was not reported.

The first prospective study failed to find epidemiological evidence to implicate an underlying prothrombotic state in IIH. (Backhouse, 2001) 25 of 30 IIH patients with normal MRV had normal thrombophilia screens and the remaining five had minor abnormalities that were not significant when compared to a control population of 90. More recently, a consecutive case study by Glueck et al (2005) compared serologic coagulation measures and polymerase chain

reaction (PCR) for five gene mutations in 65 women with IIH to 102 healthy female controls. Significantly more women in the IIH group possessed one of the gene mutations known to be associated with arteriel and venous thrombosis. Other significant findings were thrombophilic high concentrations of factor VIII present in 14 IIH cases, compared with none of the controls and an increased concentration of lipoprotein A, associated with hypofibrinolysis, in 19 patients but only 3 controls. The results may have been influenced by the high prevalence of polycystic ovary syndrome; 37 (57%) of the IIH cohort met the 2003 diagnostic criteria for the condition.

There is little evidence as yet to reliably link IIH with any specific haematological abnormality. More research is needed to determine whether stenoses in the cerebral venous sinuses have a causative role in cases of truly 'idiopathic' intracranial hypertension and to determine the prevalence of previously undetected thromboses in the condition. In addition, the possibility that a pro-thrombotic state may influence the absorption of CSF at the level of the arachnoid villi in some cases of IIH warrants further study.

1.2.2 Endocrine abnormalities

Whatever the pathological mechanism may be in IIH, it must explain the predilection of the disorder for obese women of child-bearing age. The consistent diagnosis of high numbers of such patients has focussed interest on a possible endocrine basis for the condition, with the sex hormones being obvious candidates. Furthermore, the metabolism of sex steroids is influenced by the adipose tissue and the metabolic effects of obesity vary according to gender and menopausal status.

Studies of endocrine function in patients with IIH have involved only small numbers of patients. In 15 patients with IIH, conventional tests of anterior and posterior pituitary function and peripheral target glands did not show significant abnormalities, except for a slight reduction in the growth hormone (GH) response to hypoglycaemia. (Sorensen et al., 1986a) Subnormal GH responses were also shown by Reid and Thomson (1981) in three of five patients with chronic IIH, but the response was also seen in one of the obese control patients and can occur in healthy, overweight people.(Sorensen et al., 1986a) Post-mortem examinations of arachnoid villi and human choroid plexus have demonstrated somatostatin receptors which may affect local CSF dynamics. (Katz et al., 2002) The neuropeptide somatostatin, a hormone that inhibits the release of growth hormone, has been suggested to play an as yet undefined role in the elevation of the CSF pressure in IIH, supported by reports of the successful use of its long-acting analogue, octreotide, in the condition. (Antaraki et al., 1993)

Water permeability in several biological membranes and brain water content is affected by another hormone, arginine vasopressin (AVP). In two studies by Sorensen et al, the concentration of AVP in the CSF was found to be significantly elevated in patients with IIH, despite similar plasma osmolality and AVP levels in patients and controls. (Sorensen et al., 1986a; Sorensen et al., 1982) A similar result was reported in a further study of 15 patients and 16 controls, but when CSF pressure measurement was included, no direct relationship between that and the CSF AVP level was demonstrated. (Seckl and Lightman, 1988) The importance of this seemingly consistent finding to the pathogenic processes in IIH is not known; the increased AVP may be either a cause or a result of the raised intracranial pressure, if it is connected at all.

A number of small studies have implicated steroid hormones in the aetiology of IIH. Glucocorticoids and sex steroids affect the transport capacity in the choroid plexus and may have marked effects on intracranial pressure dynamics, as shown in rabbit studies by Lindvall-Axelsson et al. (1990) Daily treatment with betamethasone significantly reduced the formation of CSF when compared with untreated controls. The reduced CSF formation was mirrored by reduced uptake of choline and a lower ATP-ase activity in the choroid plexuses of the lateral and third cerebral ventricles. Progesterone treatment of oestrogen-primed rabbits, but not oestrogen alone, had a similar effect.

Extraovarian production of oestrone has been proposed as a factor in the menstrual dysfunction reported by some obese women with IIH. (Donaldson and Binstock, 1981) Donaldson and Horak (1982) reported oestrone levels in the CSF of six obese young women with IIH in the range of 38 to 815 picograms per ml, compared to levels of less than 5 in five control patients. After treatment with dexamethasone and a low-calorie diet, three of the patients were shown to have suppression of these high CSF oestrone levels, accompanying clinical improvement, despite little change in their serum oestrone levels. Oestradiol and oestriol were not detected in the CSF, which may simply reflect the low sensitivities of the assays used. Raised CSF oestradiol, as well as oestrone, was found in a study of five IIH patients by Toscano et al. (1991) These abnormalities were accompanied by reductions in testosterone, androstenedione, and ratios of androstenedione to oestrone and testosterone to oestradiol in the CSF, when compared with 12 control patients. Plasma levels of all hormones were comparable between patients and controls.

Despite the findings of initial studies and the evidence linking polycystic ovary syndrome with IIH, (Glueck et al., 2005) the notion that abnormalities of sex steroids or indeed any

hormones underlie the disease process in IIH remains unproven. Adipose tissue is now regarded as an actively secreting endocrine organ and is considered separately below.

1.2.3 Obesity and pathogenesis

The exact mechanisms behind the high incidence of obesity in IIH are elusive. The theory of Sugerman et al (1997) of raised intracranial pressure as a direct result of intra-abdominal pressure requires the presence of centrally distributed obesity. It fails to account for the high preponderance of females in IIH, because women are less likely to have a central, androgenic distribution of their body fat than men. The metabolic and endocrine features of the obese state appear to offer greater potential to explain the disease process in IIH.

Ghrelin is a hormone with significant effects upon appetite and energy balance that has been studied in IIH. A peptide derived predominantly from the stomach, it acts as on the arcuate nucleus as a potent stimulus to the consumption of calories. (Seckl, 2004) Subramanian et al (2004) analysed fasting plasma levels in 65 patients with the condition, of which 68% were defined as being obese. The results were compared with those from a control population of 25, 76% of whom were obese and no significant differences were detected between the two groups.

In vitro and in vivo studies of serum, CSF and adipose tissue have shown obesity to be associated with chronic, low grade inflammation and an abnormal, pro-inflammatory cytokine profile. (Straczkowski et al., 2002; Dandona et al., 1998; Panagiotakos et al., 2005; Straczkowski et al., 2006) This inflammatory response is thought to have causative links with diabetes, cerebrovascular disease, asthma, and cancer. (Wellen and Hotamisligil, 2005) Adipose tissue, now regarded as an endocrine organ, secretes a wide variety of proteins

including pro-inflammatory cytokines, chemokines and hormones. Activated adipose tissue recruits macrophages that are thought to contribute to the production of inflammatory mediators. (Weisberg et al., 2003) The principal cytokines include tumour necrosis factor alpha (TNFα),(Park et al., 2005) interleukin-1 beta (IL-1β), (Maedler et al., 2002) interleukin-6 (IL-6), (Vozarova et al., 2001) interleukin-8, (IL-8) (Straczkowski et al., 2002) monocyte chemoattractant protein-1 (MCP-1), also known as CC-chemokine ligand-2, (CCL2), (Sartipy and Loskutoff, 2003) hepatocyte growth factor (HGF), (Bell et al., 2006) nerve growth factor (NGF) (Nisoli et al., 1996) and plasminogen-activator inhibitor type 1 (PAI-1). (De Pergola and Pannacciulli, 2002) Amongst the most abundantly secreted cytokines are those secreted by the adipose tissue, the adipokines leptin and adiponectin. Adiponectin, also synthesised by adipose tissue, circulates at higher concentrations in human serum than leptin. (Tilg and Moschen, 2006) Unlike leptin, adiponectin levels are reduced in obesity (Cote et al., 2005) and its actions are predominantly anti-inflammatory. (Berg and Scherer, 2005) The major role of adiponectin appears to be in enhancing insulin sensitivity. (Berg et al., 2002) The roles of other, less abundant and more recently discovered adipokines such as resistin are still debated.

1.2.3.1 Leptin

Leptin is a single chain peptide hormone comprised of 167 amino acids, synthesised predominantly by adipocytes. (Meier and Gressner, 2004) It has a number of diverse physiological functions, including roles in haematopoiesis, bone formation and initiation of puberty. (Tilg and Moschen, 2006) It is a potent pro-inflammatory cytokine that is known to influence both innate and adaptive immunity. (Aleffi et al., 2005) The major role of leptin,

however, is in the modulation of appetite and energy balance. (Klok et al., 2007) A product of the Ob gene, its name is derived from the Greek word meaning thin. Studies in mice with mutations of the Ob gene showed that severe obesity and hyperphagia exists amongst homozygous Ob/Ob animals, in which no leptin is produced. (Rohner-Jeanrenaud and Jeanrenaud, 1996) Administration of leptin results in cessation of over-eating and loss of weight. In most obese humans, however, no such genetic mutation exists and leptin levels are actually elevated. (Schwartz et al., 1996)

The hyperleptinaemia in obesity shows strong positive correlations with body fat mass. In a study of 136 lean and 139 obese people, not only was this correlation demonstrated, but the Ob messenger ribonucleic acid (mRNA) content was approximately twice as high in overweight as compared to normal weight subjects, suggesting that changes in body fat are translated into changes in serum leptin at the level of Ob gene expression. (Considine et al., 1996) The relationship between body fat and leptin suggests that sensitivity to the actions of leptin is reduced in obesity; adipocytes produce more leptin when adipose tissue mass is greater, yet this results in the increased adipose tissue mass being maintained. In other words, leptin resistance could explain the failure of obese individuals to respond to their elevated leptin levels.

A number of leptin receptors have been identified, with many isoforms, including a soluble receptor which can be measured by enzyme-linked immunosorbent assay (ELISA.) (Meier and Gressner, 2004) Levels of this soluble receptor, which acts as one of several leptin binding proteins, have also been shown to increase with increasing BMI. In lean people, most of the leptin circulates in the bound form, but in the obese, levels of free leptin are significantly increased. Total concentrations of leptin thus show less of a difference between

slim and overweight individuals than if free concentrations are measured. Leptin also exhibits circadian variation, rising to its highest levels during the night.

Caloric restriction reduces the serum leptin and the amount of adipocyte mRNA, whilst re-feeding increases these levels. (Considine et al., 1996; Rohner-Jeanrenaud and Jeanrenaud, 1996) A reduced calorie diet, resulting in weight loss, has been shown to significantly reduce serum leptin concentrations as well as levels of the soluble leptin receptor amongst healthy humans. (Wolfe et al., 2004) The leptin responses to changes in eating patterns are too rapid to be fully explained by changes in adipose mass. Acute fasting depletes the serum leptin concentrations and massive overeating has the opposite effect, both within about seven hours and despite little or no change in fat mass. (Fried et al., 2000) Acute signals must also be involved in regulating the rate of leptin secretion. The actions of leptin are to suppress food intake and to increase energy expenditure and one link between leptin and food intake is said to be the hypothalamic appetite-stimulating hormone, neuropeptide Y (NPY). (Rohner-Jeanrenaud and Jeanrenaud, 1996) Leptin is able to cross the blood-brain-barrier and binds the Ob-Rb receptors in the arcuate, ventromedial, paraventricular and dorsomedial nuclei of the hypothalamus, signalling satiety via neurons expressing NPY as well as agouti-related peptide. (Mercer et al., 1996) Thus peripheral hormonal signals are translated into the neural messages that alter appetite. (Seckl, 2004) Figure 1.13 shows a diagrammatic representation of this hypothalamic appetite regulation. Studies of severely obese rats with a genetic absence of leptin receptors showed that signalling within the arcuate nucleus limits food intake on a meal-to-meal basis, by regulating the hindbrain response to short-acting satiety signals. (Morton et al., 2005) Such a mechanism could

explain how changes of body adiposity relate to modifications in the intake of energy during individual meals.

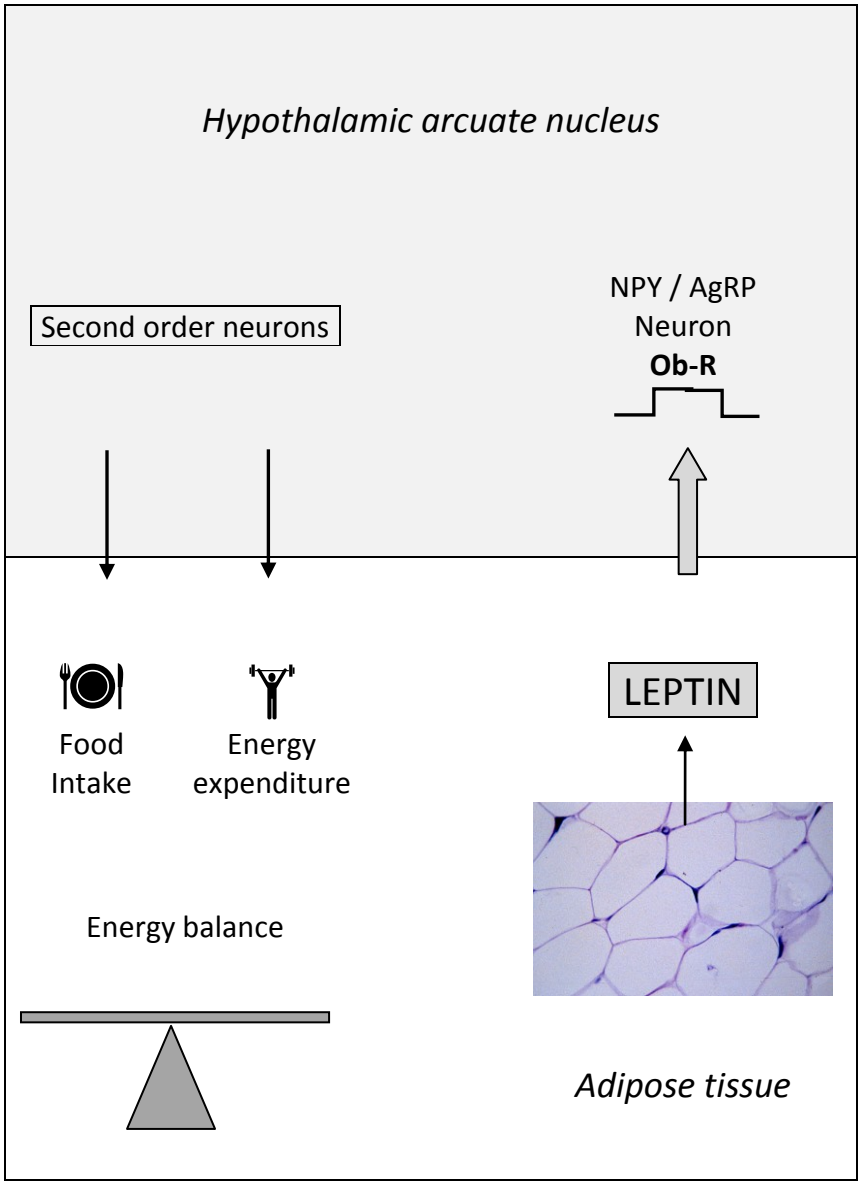


Figure 1.13: Hypothalamic appetite regulation by leptin. The arcuate nucleus is the main target of leptin, a peripheral anorexigenic signal secreted from adipose tissue. Leptin decreases NPY release to suppress appetite and body weight. Ob-R = leptin receptor, AgRP = agouti-related peptide.

Measurement of leptin in the CSF is possible, and gives an indication of how the adipose-secreted hormone is transported into the brain, although some leptin may be produced centrally. (Meier and Gressner, 2004) CSF leptin concentrations increase with higher values of BMI, but the correlation is not as strong as that seen with plasma levels. (Caro et al., 1996)

CSF leptin also does not appear to show a circadian rhythm; a study in which CSF was sampled from 9 volunteers, every 30 minutes over a 24-hour period, failed to show diurnal variation in the levels. (Wong et al., 2004) Schwartz et al (1996) demonstrated that whilst CSF leptin, in 53 human subjects, correlated positively with plasma levels, the relationship was non-linear and the ratio of CSF to plasma leptin was lower amongst people with the highest plasma leptin concentrations. Caro et al (1996) found that 23 lean subjects had a mean CSF to serum ratio over four-fold higher than their eight obese counterparts, who had only a 30% increase in their CSF leptin, despite a mean serum level 318% higher. A similar study found a 2.3 times higher ratio of CSF to serum leptin in 14 normal weight than 16 obese women, and also showed that after significant weight loss, both CSF and serum levels were reduced. (Nam et al., 2001) Others have documented a negative association between the ratio of CSF to serum leptin and both BMI and serum leptin. (Rodrigues et al., 2002) It would appear that the relationship between CSF and plasma leptin is not a straightforward one. It can be described logarithmically, and may reflect a reduction in the efficiency of leptin's delivery into the brain in obese individuals. Some authors have argued for the presence of a saturable transport system or even a separate mechanism in response to the hyperleptinaemia of obesity. (Schwartz et al., 1996; Hagan et al., 1999)

Although the amount of leptin is dependent upon the mass of its secretory organ, the adipose tissue, some people exhibit lower or higher levels than predicted from their body fat and there is considerable inter-individual variation. Age, ethnicity, and basal glucose concentrations do not influence circulating leptin concentrations, but levels do show a sexual dimorphism. Leptin levels are greater in women than men, even when corrected for absolute measures of fat mass. (Rosenbaum et al., 1996; Rosenbaum and Leibel, 1999) In

vitro adipose tissue cultures have shown that secretion of leptin by samples from female donors is significantly higher than those from males, despite no gender differences in adipocyte number or size amongst the omental tissue samples. (Casabiell et al., 1998; Menendez et al., 2000) The secretion of leptin by the omental fat in these studies was not correlated with the BMI of the donors. Furthermore, the pulse amplitude of leptin release has been shown to be two to three times higher in women than men, although there was no apparent sex difference in the frequencies of leptin pulses. (Rosenbaum and Leibel, 1999) There are associations between leptin and sex hormones. Leptin receptors occur in the peripheral reproductive organs and are also found on hypothalamic neurones that control reproductive function, as well as energy balance. (Casabiell et al., 2001) Leptin appears to integrate systems of energy homeostasis with those controlling the hypothalamic-pituitary axis, via complex and reciprocal interactions. (Rosenbaum and Leibel, 1999) There is evidence that it regulates the synthesis and secretion of GnRH, gonadotrophins and sex steroids and that its reduction during periods of fasting mediates the suppression of reproductive hormones. (Ahima, 2004)

Adipose tissue contains oestrogen, androgen, and progesterone receptors and the gonadal steroids account for differences in the distribution and amount of adipose tissue between males and females. (Rosenbaum and Leibel, 1999) Whilst leptin and oestradiol appear to interact to affect fat metabolism, there is evidence that oestradiol's regulation of the secretion or action of leptin is not a direct effect, and that the converse is true. (Pelleymounter et al., 1999) Adipocytes from male donors, studied in vitro, appear to be refractory to the action of steroid hormones in terms of leptin secretion. (Casabiell et al., 2001) In samples from female donors however, leptin levels have been shown to rise

significantly in response to oestrogen, and secretion seems to be inhibited by androstenedione, dihydrotestosterone and dehydroepiandrostene sulphate (DHEA).

There appears to be a dynamic relationship between leptin and the reproductive system, with leptin behaving as a hormonal messenger, coordinating nutritional status and reproductive function. It may thus act as an afferent signal, carrying information about somatic energy stores, whilst itself being influenced by adipose mass and sex hormones. (Rosenbaum and Leibel, 1999) Homozygous Ob/Ob mice, which cannot produce leptin, remain in a pre-pubertal stage and are sterile, despite a normal early sexual differentiation. (Casabiell et al., 2001) The situation can be reversed if pure, recombinant leptin is repeatedly administered. Leptin concentrations vary throughout the normal menstrual cycle; levels in the luteal phase are significantly higher than in the follicular phase and there is some experimental evidence to suggest that in the presence of pre-ovulatory levels of oestrogen, progesterone can stimulate leptin secretion. (Messinis et al., 2001) In studies of elite female athletes, low oestradiol levels accompanied reduced plasma leptin levels, which themselves were more markedly low amongst amenorrhoeic than cyclical women. (Thong et al., 2000) Administration of recombinant human leptin can reverse features of hypothalamic amenorrhoea. (Welt et al., 2004) In pregnant women plasma leptin levels are elevated, in the absence of increased food intake, which suggests there may be a temporary, acquired resistance to its effects. (Casabiell et al., 2001) The precise role of leptin in pregnancy and in the menstrual cycle is unclear, but the relationship between BMI and leptin is certainly altered during pregnancy and throughout the normal menstrual cycle. (Hardie et al., 1997) It has been suggested that the apparent leptin insensitivity seen amongst pregnant women may function to encourage increased energy intake during gestation.

Leptin also shows an interaction with corticosteroids. Cortisol, the major glucocorticoid synthesised and released by the human adrenal cortex, has a variety of effects upon metabolism. A significant positive association has been demonstrated between 24-hour urinary free cortisol and concentrations of leptin in CSF and to a lesser extent plasma. (Hagan et al., 1999) There is evidence from animal experiments that leptin can act at the level of the adrenal gland to inhibit the production of cortisol. (Bornstein et al., 1997) In addition, glucocorticoids affect the release of leptin. A study of 52 human subjects showed a significant increase in plasma leptin levels following treatment with the synthetic corticosteroid dexamethasone compared to placebo. (Dagogo-Jack et al., 1997) High levels of glucocorticoids are known to be associated with hyperphagia and weight gain and may exert their effects on fat deposition via the production of, or sensitivity to, leptin.

A receptor for the hormone leptin has been cloned from the site of CSF production, the choroid plexus. (Tartaglia et al., 1995) There has been speculation that patients with IIH may have disturbed leptin function, or that the adiposity-related hormone may have a role in the pathogenesis of IIH. In a study by Lampl et al (2002) serum leptin concentrations of 15 patients with IIH were measured under conditions of food restriction. All the patients were female and obese. Results were compared to those from 16 obese and 15 non-obese, female controls. The patients with IIH had significantly higher serum leptin concentrations than either control group. As expected, the serum leptin levels were significantly associated with BMI amongst the control subjects, but in patients with IIH this association did not persist. The authors propose that additional factors may be involved in the hyperleptinaemia in IIH, beyond obesity, possibly hypothalamic in origin. In the study primarily examining ghrelin in

IIH, Subramanian et al (2004) also measured fasting serum leptin, and found that patients had significantly higher levels than controls.

Mysteries surround the pathogenesis of IIH and its relation to obesity and female gender. Not all obese females develop IIH, and the condition can occur in males, children and individuals of normal weight. However, the consistent predominance of overweight women of reproductive age amongst cohorts of patients with IIH demands explanation, and possible links with sex hormones and leptin warrant further study.

CHAPTER 2 CYTOKINE PROFILES IN IIH

2.1 Background

Although the pathophysiology of IIH remains unknown, it is not traditionally regarded as an inflammatory disorder. The majority of patients with IIH are overweight, however and can be expected to exhibit the low-grade, chronic inflammatory response of obesity. Cytokines and other immune mediators have not been studied in IIH, with the exception of leptin, as discussed in chapter 1. The hypothesis that IIH may be defined by a pro-inflammatory cytokine profile in both serum and CSF is worthy of exploration. Additionally, adipokine dysregulation may represent a causative factor in the underlying IIH disease processes including the raised intracranial pressure.

In order to investigate this, adipokines and inflammatory cytokines were analysed in paired serum and CSF from patients with IIH and compared to samples from patients with other neurological disorders.

2.2 Methods

2.2.1 Patients

Patients with IIH and control subjects were recruited at University Hospital Birmingham NHS Foundation Trust and Sandwell & West Birmingham Hospitals NHS Trust. All patients underwent lumbar puncture as part of their routine clinical care. Patients with IIH were recruited at the time of initial presentation, following the confirmation of elevated CSF opening pressure at lumbar puncture. A small number of patients were included who had

established IIH and were being investigated following a clinical deterioration. All patients were diagnosed according to the updated criteria. (Friedman and Jacobson, 2002)

Control subjects consisted of a heterogeneous group of patients under investigation for neurological illnesses. Patients were invited to take part in the study when having an elective lumbar puncture as part of their routine clinical care. A subset of control subjects were matched with IIH patients for gender, age (±5 years) and BMI (±2 kgm^{-2}). Patients with acute infections or relapse of known disease were excluded and controls were screened for signs or symptoms of IIH. Subjects were also excluded if aged less than 16 years or if unable to give written informed consent.

Permission for the study was obtained from the North West Multi-Centre Research Ethics Committee and all participants gave written informed consent.

Clinical details including medical history, current medication and results of imaging were noted for each subject. The following anthropological measures were recorded: weight, height, waist and hip circumference. BMI was calculated as weight in kg/ height in m^2.

2.2.2 Samples

All lumbar punctures were carried out with the patient in the left lateral position, whilst breathing regularly. (Neville and Egan, 2005) CSF opening pressure was measured to the nearest 0.5cm by direct manometry. CSF and blood samples were collected at the time of lumbar puncture and transported on ice before being promptly centrifuged at 1500 rpm for 10 minutes and aliquoted. All samples were stored at -80˚C and analysed after a maximum of one freeze-thaw cycle.

2.2.3 Multiplex immunoassay

Cytokines were measured using multiplex detection immunoassays. This is a validated method enabling quantitative determination of several cytokines. (Ooi et al., 2006)

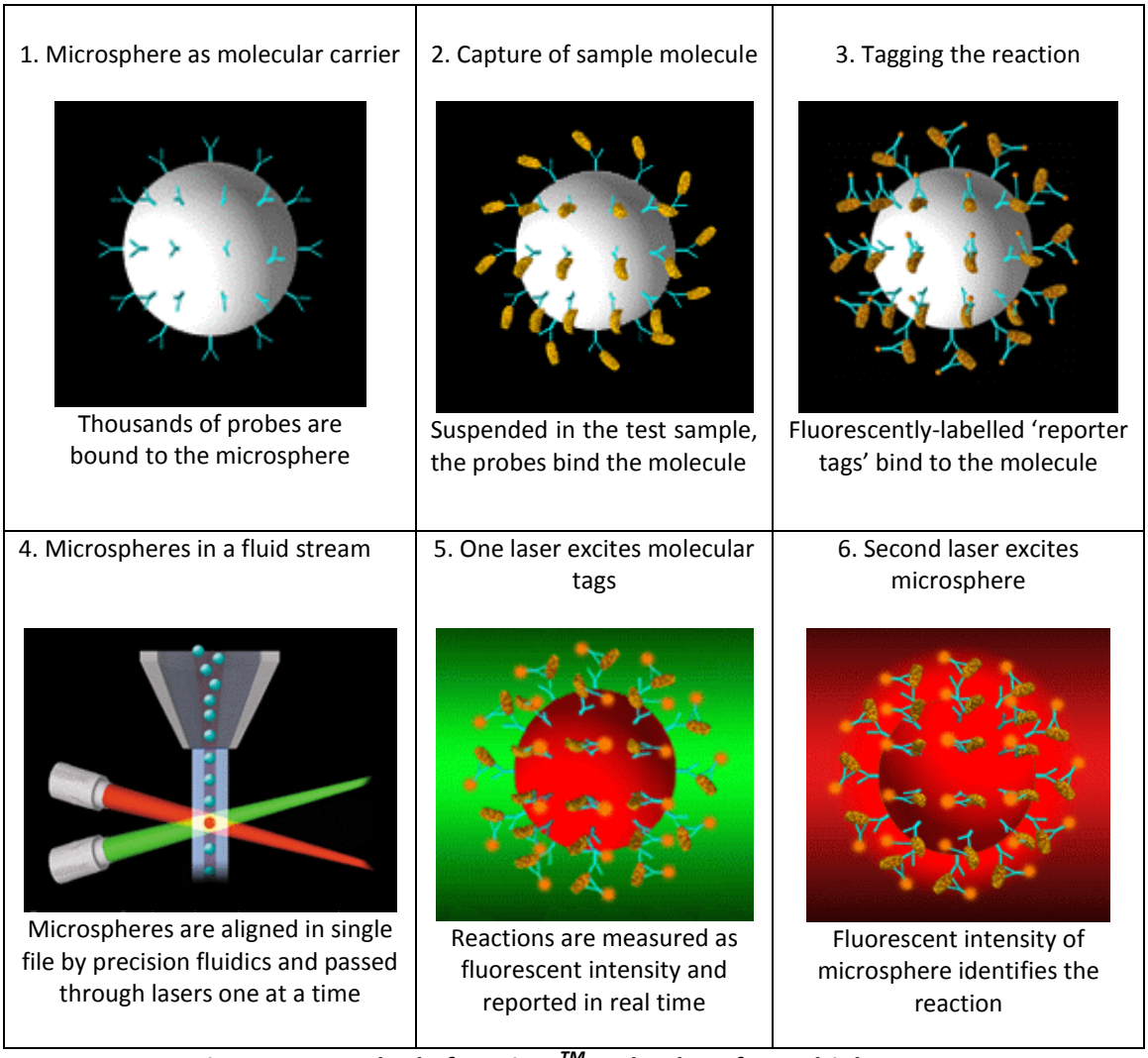


Figure 2.1: Method of Luminex™ technology for multiple assays

The technology involves a process that dyes latex microbeads with a blend of different fluorescent intensities of two dyes. Using precise ratios, numerous different bead sets are created, each one being unique and distinguishable in a laser beam, based on the "colour code" that results from the ratio of the two dyes. These beads are the foundation for the immunoassay. Capture antibody for a specific molecule is coupled to a specific bead set.

After an analyte is bound to the capture antibody on the bead, a detector antibody is used as a reporter. The detector antibody is coupled to phycoerythrin, a red protein from the light-harvesting phycobiliprotein found in some bacteria and algae. The end result is an antibody sandwich assay on the colour coded microbead. The beads and the reporter molecule are read on a Luminex^{TM} 100 instrument using a dual laser system as they pass through a flow cell. One laser detects the beads (the colour code for an assay) and the other laser detects the reporter signals. This is summarised in Figure 1.1.

By using multiple bead sets, multiple assays can be conducted simultaneously. Each unique assay is identified by the colour code for the bead on which the assay is built, and the amount of the analyte is determined by the reporter signal. The Luminex^{TM} 100 instrument has advanced optics to capture the colour signals, and translate them into real time quantitative data for each reaction.

2.2.4 Cytokines

Two commercial kits were used (Linco Research, Millipore, Billarica, USA), each measuring a panel of adipokines as shown in table 2.1. Panel A contained a mixture of three bead populations with distinct fluorescence, coated for antibodies specific for resistin, adiponectin and plasminogen activator inhibitor-1 (PAI-1). Panel B contained nine bead populations specific to the adipokines listed, including leptin.

Serum samples were diluted x400 with assay buffer for the measurement of resistin, adiponectin and PAI-1 due to the higher reference concentrations of these adipokines in humans. The precision of the assay was defined by a quoted intra-assay variation of 1.4 – 7.9%.

Table 2.1 Human Adipokine Panels with detection ranges

	Adipocytokine	***Abbreviation***	***Detection Range pgml^{-1}***
Panel A	Resistin		3 – 12500
	Adiponectin		1600-10^8
	Plasminogen activator inhibitor	PAI-1	10-100000
Panel B	Leptin		100-62500
	Interleukin 1-beta	IL-1β	0.6 – 625
	Interleukin 6	IL-6	0.6 – 2500
	Interleukin 8	IL-8	0.6 – 2500
	Tumour necrosis factor alpha	TNFα	0.6 – 2500
	Monocyte chemotactic protein 1	MCP-1	20 – 1000
	Hepatocyte growth factor	HGF	100-2500
	Nerve growth factor	NGF	20-4000
	Insulin		100-10000

For all assays, 25 µl samples were incubated with antibody-coated capture beads for two hours at room temperature. Beads washed with assay buffer were further incubated with biotin-labelled anti-human cytokine antibodies for 30 minutes followed by streptavidin–phycoerythrin for 30 minutes. Samples were analysed using a Luminex 100™ (Luminex, Austin, Texas, USA) with Starstation™ software (Applied Cytometry Systems, Sheffield, UK). Identified reactions were recorded as numbered events for each analyte. Standard curves of known concentrations of recombinant human cytokines were used to convert fluorescence units to cytokine concentration. (Curnow et al., 2005)

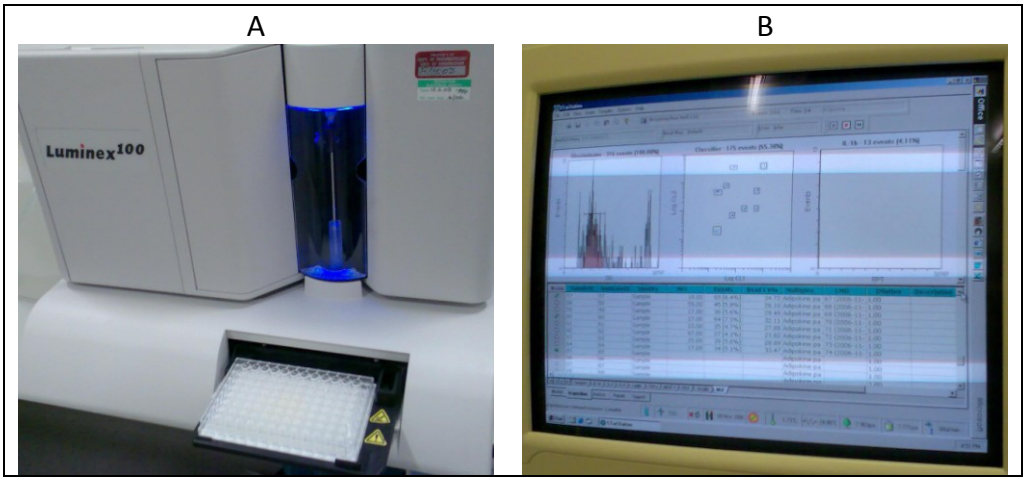


Figure 2.2 A: LuminexTM 100 machine used for the multiplex assays, B: PC monitor with Starstation™ software processing the event data for one of the analytes, IL-1β

2.2.5 Statistical Analysis

Statistical analysis was performed using SPSS version 14 (SPSS Inc., Chicago, IL, USA) and Prism for Windows Version 5.0 (GraphPad Software Inc, San Diego, CA, USA) software packages. Continuous data were summarised using means and standard deviations (or medians and ranges for non-normally distributed data).

Cytokine levels in the IIH group and in controls were compared using a two-tailed, non-parametric t-test (Mann-Whitney U). Cytokine levels in the separate diagnostic groups were compared using a one-way ANOVA, with Dunnett's post hoc test for parametric data, or a Kruskal-Wallis analysis with Dunn's test for non-parametric data. Multivariable regression models were used to examine the effects of variables age, gender, BMI and diagnostic group on cytokine levels. Associations between cytokine levels and clinical parameters were analysed using Pearson correlation for parametric data and Spearman rank correlation for non-parametric data. The level at which the results were judged significant was $p < 0.05$.

2.3 Results

2.3.1 Patient characteristics

Serum and CSF specimens were collected from 88 patients. Patient characteristics are shown in Table 2.2. Of the 26 patients with IIH, 22 were newly diagnosed cases and four patients had established or previous IIH, with worsening symptoms as the indication for lumbar puncture.

Table 2.2: Patient characteristics.

	IIH (n=26)	Controls (n=62)	p value
Age [a]	28.7 ±7.73	47.9 ±13.64	<0.0001
BMI [a]	35.1 ±5.5	28.2 ±7.3	<0.0001
Female (%)	100	64	<0.0001
Waist circumference [a] (cm)	99.1 ±16.2	94.9 ±17.1	0.2
Waist-hip ratio [a]	0.87 ±0.08	0.91 ±0.11	0.12
Opening Pressure [a] (cm CSF)	35.3 ±6.7	18.5 ±7.6	<0.0001

[a] *mean ± standard deviation*

The IIH patients were younger ($p < 0.0001$), had higher BMI ($p < 0.0001$) and higher CSF opening pressures ($p < 0.0001$) than subjects in the control group. The control subjects comprised patients with a confirmed diagnosis of multiple sclerosis (MS) (12), from whom samples were collected during disease remission, cerebrovascular disease (CVS) (10) and mixed neurological diseases (MIX) (28). In addition, 12 patients who had presented with functional neurological symptoms for which investigation of CSF was clinically justified, but who had no neurological diagnosis and normal neurological investigations two years after recruitment, were included as controls (N). Table 2.3 shows the characteristics amongst the individual diagnostic groups. Table 2.4 shows the primary diagnoses amongst the MIX control group.

When the diagnostic groups were considered separately, patients in the IIH group were significantly younger, more overweight and had higher CSF opening pressure than patients in all of the control groups (N, MS, CVS and MIX groups.)

Table 2.3: Patient characteristics by diagnostic group

	IIH (n = 26)	**N (n = 12)**	**MS (n = 12)**	**CVS (n = 10)**	**MIX (n = 28)**
Age[a]	28.7 ± 7.7	42.2 ± 2.6	38.0 ± 10.4	56.1 ± 9.8	51.6 ± 14.6
Female (%)	100	75.0	75.0	40.0	64.3
BMI[a] (kgm^{-2})	35.1 ± 5.5	30.2 ± 10.5	27.2 ± 5.9	27.0 ± 4.6	28.1 ± 7.1
Waist-hip ratio[a]	0.87 ± 0.08	0.90 ± 0.09	0.88 ± 0.10	0.99 ± 0.15	0.91 ± 0.09
Opening pressure[a] (cm CSF)	35.3 ± 6.7	18.1 ± 7.2	17.1 ± 3.5	20.4 ± 7.7	18.3 ± 8.8

[a] mean ± standard deviation

N = normal investigations, MS = multiple sclerosis, CVS = cerebrovascular disease, MIX = mixed neurological diseases.

Table 2.4: Primary Diagnoses amongst controls with 'mixed neurological conditions'

Clinical diagnosis	**Number**
Headache or migraine	7
Peripheral neuropathy	4
Motor neurone disease	3
Cervical neuropathy	3
Spastic paraperesis	2
Alzheimers disease	2
Aseptic meningitis	1
Cerebral vasculitis	1
Metastatic carcinoma	1
Mixed connective tissue disease	1
Uveitis	1
Unexplained optic neuropathy	1
Unknown	1
Total	**28**

2.3.2 Cytokine analysis

Cytokines were detected in the CSF and serum of subjects to varying degrees. Table 2.5 shows the proportion of cytokines detected above minimum concentration in each diagnostic group as a percentage of the total number of assays for each cytokine (i.e. [number detected] / [number detected + number not detected] %, or [positive assays] / [positive assays + negative assays] %).

Table 2.5: Rate of detection of cytokines (%)

	Serum					***Cerebrospinal fluid***				
Cytokine	**IIH**	**N**	**MS**	**CVS**	**MIX**	**IIH**	**N**	**MS**	**CVS**	**MIX**
IL-1β	4	0	0	10	6	0	0	0	0	0
IL-6	12	25	7	22	13	86	71	75	75	74
IL-8	20	31	40	60	25	100	100	100	100	95
Leptin	100	100	93	100	100	100	87	81	100	95
TNFα	50	77	50	50	81	0	0	0	0	5
MCP-1	96	92	100	100	100	100	100	100	100	95
HGF	27	33	33	40	63	95	93	81	83	89
Insulin	38	33	15	50	25	0	0	0	0	0
NGF	35	17	13	30	38	0	0	0	0	0
Adiponectin	100	100	100	100	100	100	100	94	100	95
Resistin	96	100	100	91	100	100	100	94	100	95
PAI-1	100	100	92	90	100	100	100	93	100	100

All cytokines in the panel were detected in at least some of the samples (i.e. present at concentrations above the minimum level of sensitivity for the assay) with the exception of IL-1β, NGF and insulin, which were not detected in any CSF sample.

The range in concentrations of cytokines in the serum and CSF samples are shown in table 2.6.

The concentrations of cytokines amongst the IIH patients were compared to those amongst the whole control population, for all assays in which the detection rate was above 50%. There were no significant differences between IIH patients and controls in serum resistin, PAI-1, TNFα, HGF and CSF IL-8, MCP-1, resistin, PAI-1, HGF and IL-6 (figure 2.3). Serum concentrations of IL-8 and MCP-1 were higher in the control group than the IIH patients ($p=0.04$ and $p=0.008$ respectively.)

Table 2.6: Cytokine concentration ranges in serum and CSF (pgml^{-1} unless stated)

			Control			
		IIH	**N**	**MS**	**CVS**	**MIX**
Serum	IL-1b	<0.6 - 0.71	all < 0.6	all < 0.6	<0.6 - 0.62	<0.6 - 1.43
	IL-6	<0.6 - 10.4	<0.6 - 9.05	<0.6 - 2.16	<0.6 - 1.36	<0.6 - 2.16
	IL-8	<0.6 - 1.18	<0.6 - 2.20	<0.6 - 1.2	<0.6 - 2.63	<0.6 - 3.19
	Leptin (ngml^{-1})	1.10 - 21.88	0.13 - 6.11	<0.1 - 5.84	0.43 - 5.57	0.32 - 12.56
	TNFa	<0.6 - 3.74	<0.6 - 3.17	<0.6 - 3.1	<0.6 - 5.3	<0.6 - 4.71
	MCP-1	<20 - 434.8	<20 - 310.9	24.1 - 397.6	119.1 - 340	100.0 - 405.8
	HGF	<0.6 - 1,639.5	<0.6 - 1,066.5	<0.6 - 981.6	<0.6 - 1,114.8	<0.6 - 1,769.0
	Insulin	<30 - 366.4	<30 - 93.8	<30 - 400.4	<30 - 184.4	<30 - 159.7
	NGF	<20 - 110.8	<20 - 248.0	<20 - 70.4	<20 - 42.4	<20 - 149.3
	Resistin (ngml^{-1})	<0.003 - 77.1	2.9 - 75.3	6.8 - 53.7	<0.003 - 62.2	3.6 - 100.9
	Adiponectin (μgml^{-1})	0.261 - 58.9	4.88 - >100	0.40 - >100	0.529 - >100	3.298 - >100
	PAI-1(ngml^{-1})	3.1 - 130.8	8.2 - 152.6	<0.01 - 141.2	<0.01 - 43.5	5.7 - 138.9
CSF	IL-1b	all < 0.6	all < 0.6	all < 0.6	all < 0.6	all < 0.6
	IL-6	<0.6 - 20.3	<0.6 - 9.28	<0.6 - 27.7	<0.6 - 24.2	<0.6 - 112.5
	IL-8	4.06 - 24.7	4.78 - 25.2	3.08 - 52.1	4.15 - 31.9	<0.6 - 55.2
	Leptin (ngml^{-1})	1.10 - 5.87	<0.1 - 4.02	<0.1 - 2.42	0.14 - 5.61	<0.1 - 2.62
	TNFa	all < 0.6	all < 0.6	all < 0.6	all < 0.6	all < 0.6
	MCP-1	148.3 - 886.0	160.9 - 750.8	134.1 - 1324.9	141.2 - 1274.6	<20 - 1461.0
	HGF	<100 - 686.0	<100 - 388.2	<100 - 645.3	<100 - 624.9	<100 - 726.6
	Insulin	all < 100	all < 100	all < 100	all < 100	all < 100
	NGF	all < 20	all < 20	all < 20	all < 20	all < 20
	Resistin	35.0 - 550.0	49.2 - 522.3	<3 - 372.0	34.2 - 2,943	<3 - 1,832
	Adiponectin (ngml^{-1})	2.97 - 10.48	3.70 - 25.14	<2 - 26.03	3.70 - 25.14	<2 - 109.08
	PAI-1	27.0 - 254.3	24.4 - 154.0	<10 - 227.9	54.9 - 255.9	<10 - 505.3

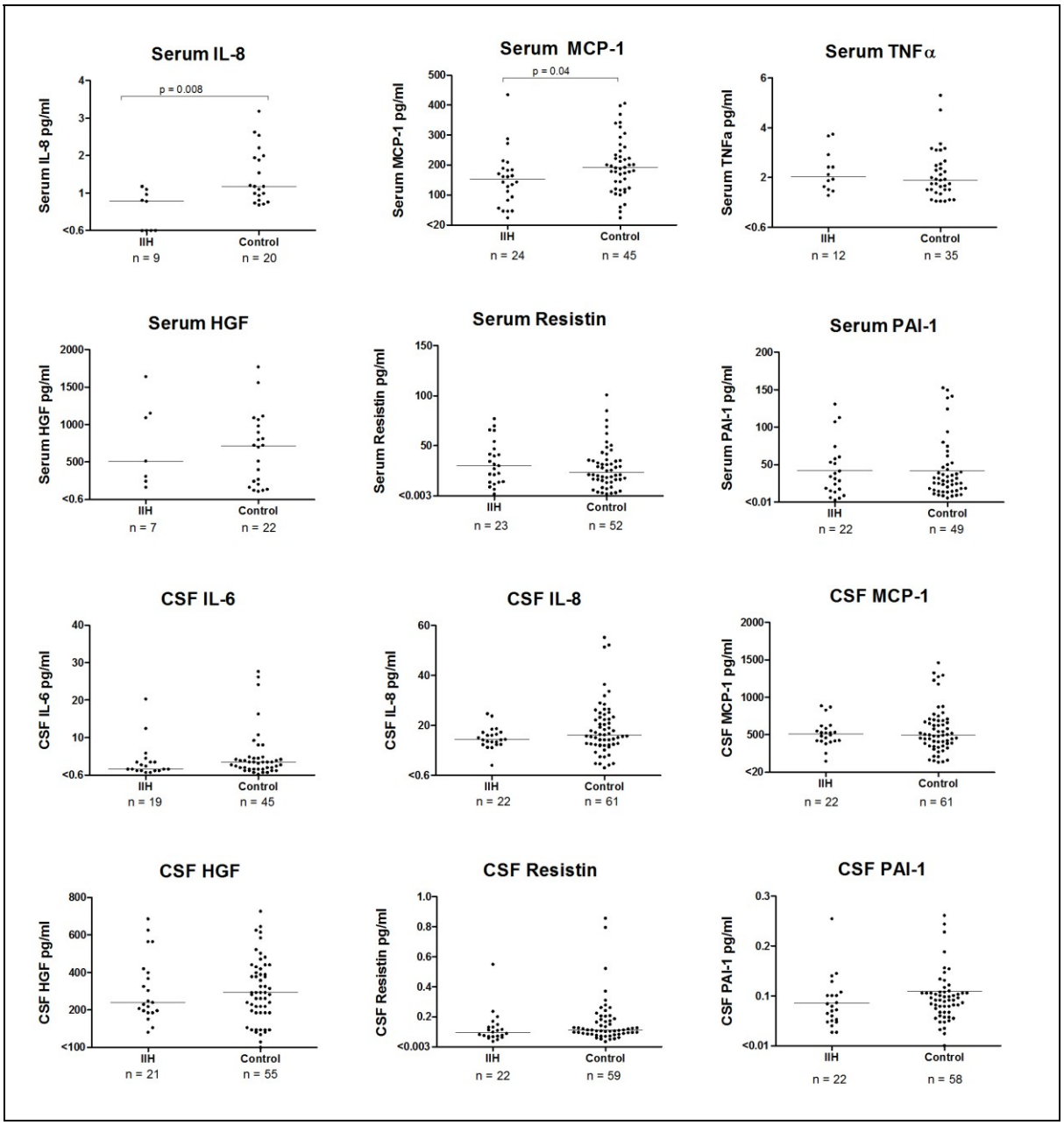


Figure 2.3: Scatter plots of cytokine concentrations in IIH patients and controls, medians shown

Serum adiponectin concentrations were lower in the IIH patients, although the difference was not significant. CSF adiponectin was significantly lower in the IIH group (p=0.0005). Serum leptin was higher amongst patients with IIH than controls, as was CSF leptin (both p<0.0001.) The results are summarised in figure 2.4.

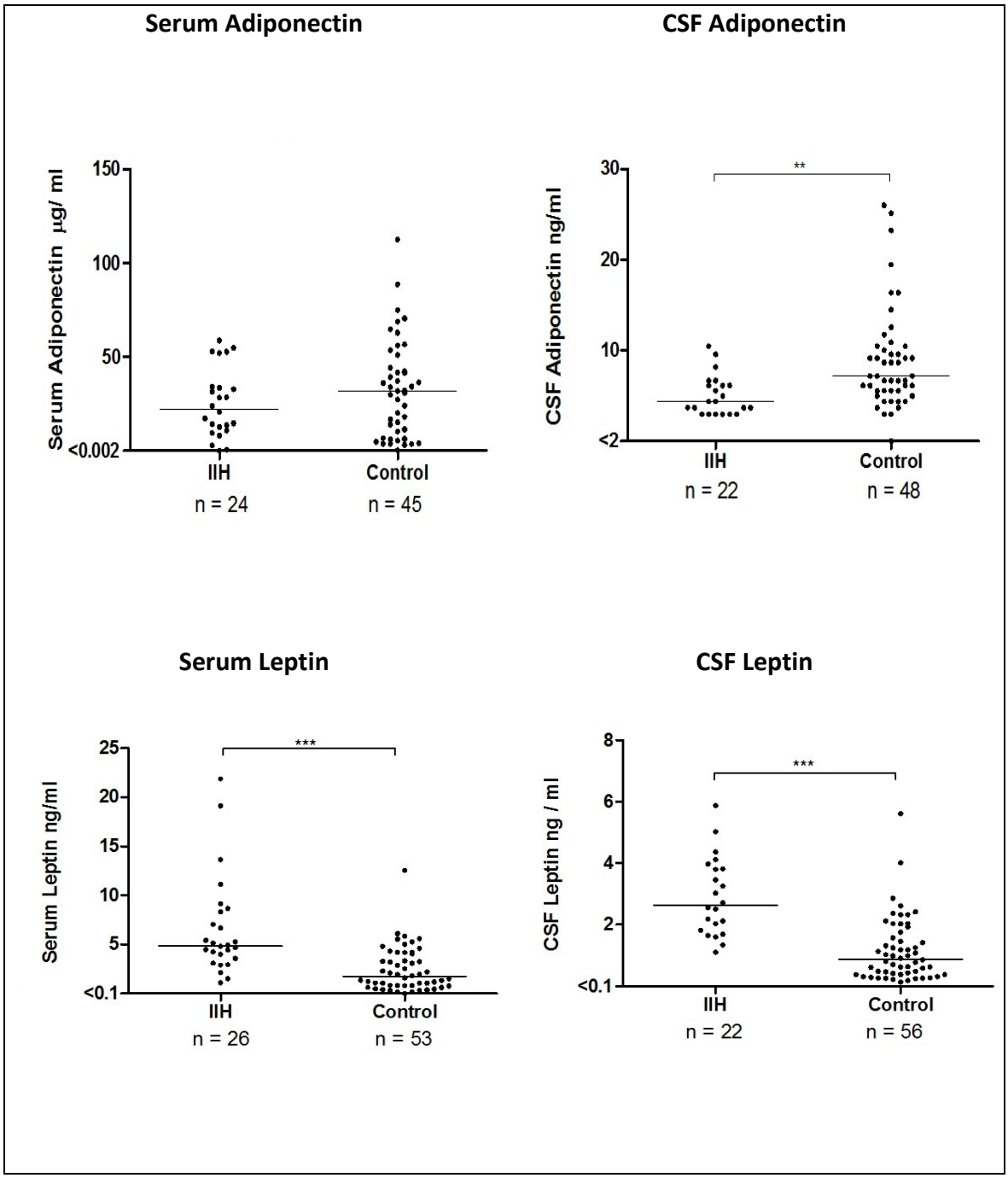


Figure 2.4: Serum and CSF adiponectin and leptin concentrations in IIH patients and controls.

2.3.3 Regression Analyses

To examine whether the differences observed were an effect of the diagnostic group itself (IIH or control), or due to other characteristics such as BMI, regression analyses were carried out. CSF adiponectin was significantly influenced by age in the multivariate regression analysis (p=0.017). The correlation of adiponectin with age was confirmed separately (Spearman r=0.46, p<0.0001). Once the regression analysis was carried out to correct for age, gender and BMI, the CSF adiponectin was no longer significantly lower in the IIH group. Serum leptin was not significantly higher in IIH patients after correction for age, gender and BMI. Serum leptin was positively influenced by BMI (p < 0.0001) and gender (levels being higher in females, p < 0.0001) in the multivariate regression (table 2.7).

				95% Confidence Interval	
	P value	**B value**	**Standard Error**	**Lower Bound**	**Upper Bound**
Diagnostic group	0.82	0.193	0.109	-0.025	0.411
Age	0.511	0.002	0.003	-0.004	0.009
BMI	<0.0001	0.029	0.006	0.017	0.040
Gender	<0.0001	0.458	0.104	0.251	0.664
Dependent variable Log 10 transformed serum leptin. R squared = 0.550					

Table 2.7: Regression model data for serum leptin

CSF leptin was significantly influenced by BMI (p<0.0001) and gender (p<0.0001). However, CSF leptin levels remained higher in the IIH group compared to controls following regression analysis to correct for these factors (p=0.001) (table 2.8).

				95% Confidence Interval	
	P value	**B value**	**Standard Error**	**Lower Bound**	**Upper Bound**
Diagnostic group	0.001	0.343	0.098	0.147	0.538
Age	0.178	0.004	0.003	-0.002	0.10
BMI	<0.0001	0.028	0.005	0.018	0.038
Gender	<0.0001	0.421	0.089	0.244	0.598
Dependent variable Log 10 transformed CSF leptin. R squared = 0.593					

Table 2.8: Regression model data for CSF leptin

Using the correction factors identified by the regression analysis, corrected CSF leptin values were compared between IIH patients and controls as shown in figure 2.5. Also shown in figure 2.5 is a scatter plot of CSF leptin values in ten IIH patients and ten controls matched for age, gender and BMI. CSF leptin was significantly elevated in the ten patients (p = 0.023) when compared to this matched control cohort.

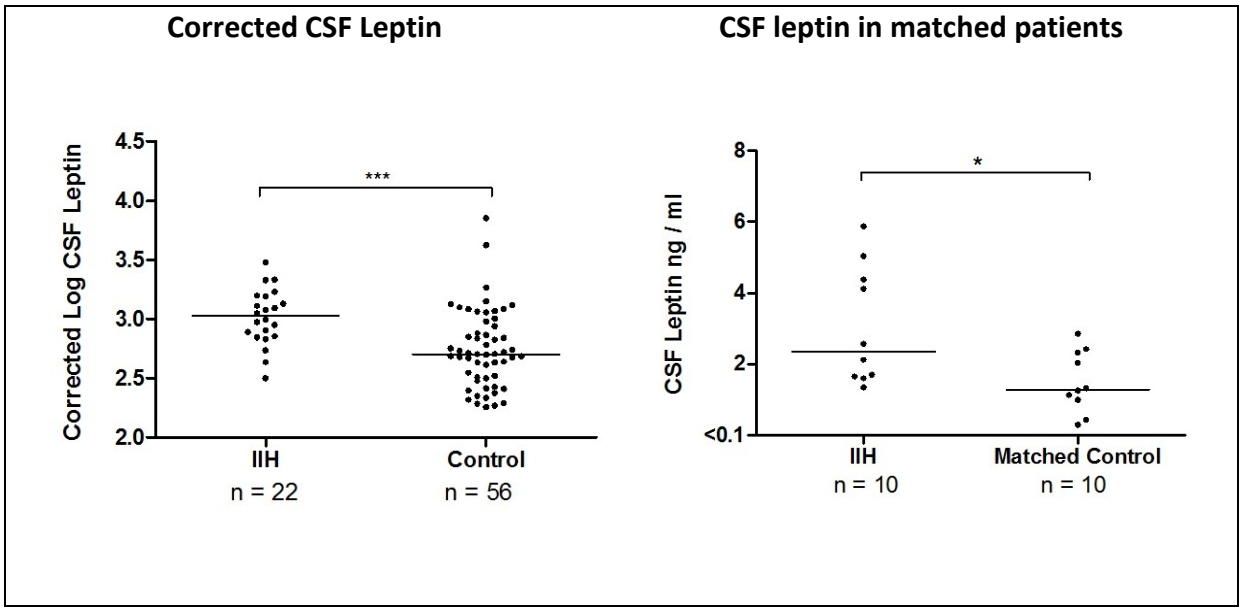


Figure 2.5: CSF Leptin after correction or matching for age, gender and BMI

2.3.4 Correlations

To further investigate the CSF leptin result, its relationship with CSF opening pressure was examined. A significant positive correlation of CSF leptin with CSF opening pressure was identified in the total cohort (Spearman r = 0.47; p < 0.0001) (Figure 2.6). However, when IIH patients and controls were analysed separately, the correlation was significant for the control population (r=0.42, p=0.005) but not for the IIH cohort (r=0.11, p=0.62).

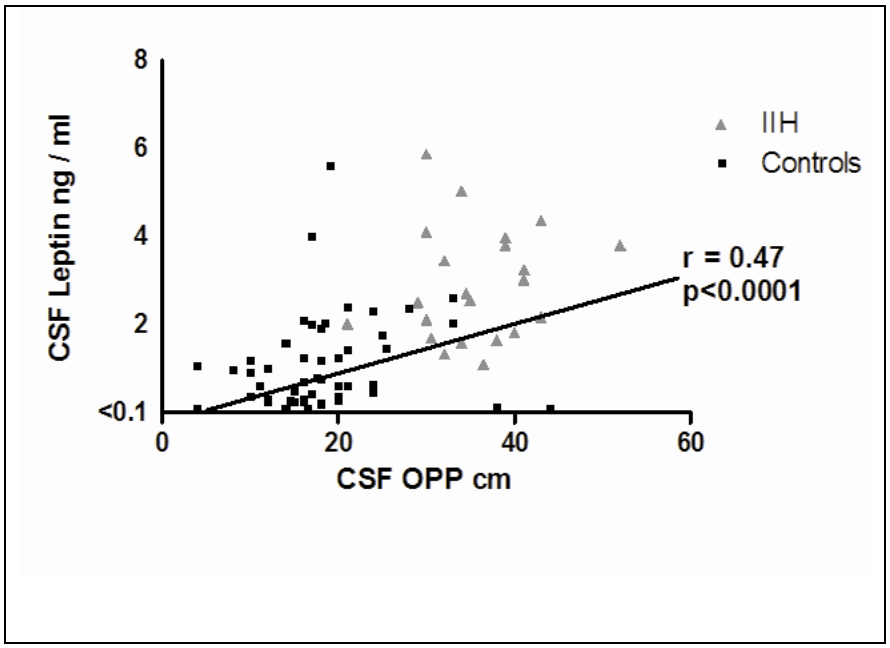


Figure 2.6: Relationship between CSF opening pressure (CSF OPP) and CSF leptin, line of best fit

The correlations between BMI and leptin concentrations were compared between IIH patients and controls. In the total control population cohort, BMI was significantly positively correlated with serum leptin (r = 0.34; p = 0.007) and CSF leptin (r = 0.51; p<0.0001), figure 2.7. This was not the case amongst the IIH population (serum leptin r = 0.09; p=0.67, CSF leptin r = 0.21; p = 0.34).

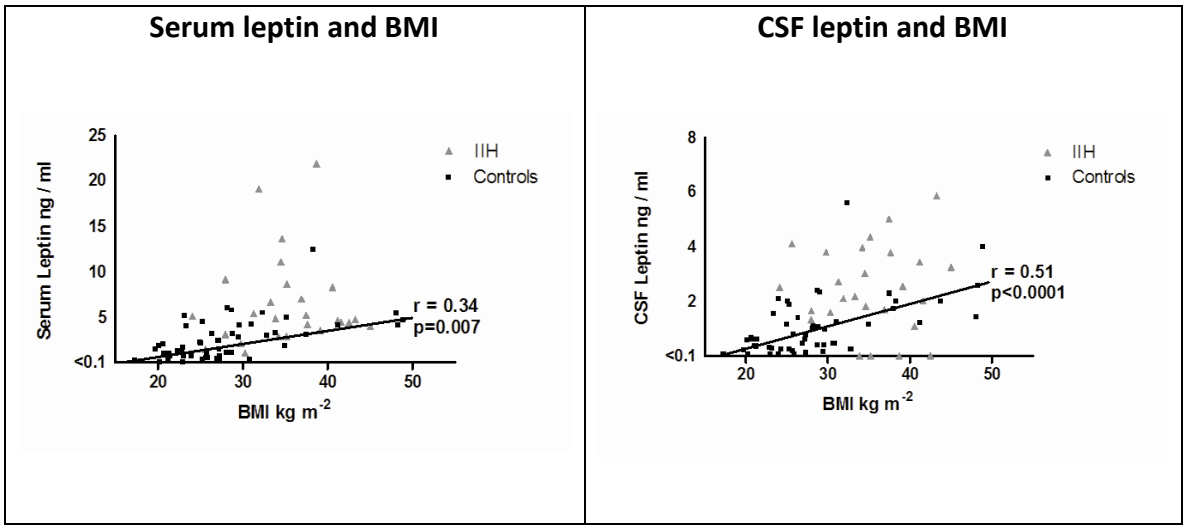


Figure 2.7: Relationship between serum and CSF leptin and BMI showing lines of best fit for control cohort

Adiponectin showed a negative correlation with BMI amongst the whole cohort. The correlation between serum adiponectin and BMI was weakly significant (r=-0.24, p=0.04) as was that between CSF adiponectin and BMI (r=-0.27, p=0.015.) When the correlations were examined with the subjects split by diagnostic group (IIH and all controls), the significance was lost.

All cytokines were examined for correlations between serum and CSF levels and BMI as well as waist circumference and waist:hip ratio. Other significant findings were negative correlations between serum IL-8 and BMI (r=-0.38, p=0.0004) and serum NGF and BMI (r=-0.22, p=0.04.) Waist circumference showed significant positive correlation with CSF IL-6 (r = 0.31; p = 0.01), CSF PAI-1 (r = 0.26; p = 0.04), CSF resistin (r = 0.26; p = 0.04), CSF leptin (r = 0.35; p = 0.006) and serum leptin (r = 0.37; p = 0.006).

2.3.5 Further Analyses

The ratio of CSF:serum concentrations were examined for IL-8, MCP-1, HGF, resistin, PAI-1, adiponectin and leptin. The ratios were not significantly different between IIH patients and controls for any adipokine. When correlations between the serum and CSF concentrations were examined for each of these seven adipokines, only leptin and resistin showed a correlation between serum and CSF levels. In the case of leptin, the serum and CSF concentrations were correlated amongst the whole cohort (r=0.66, p<0.001) and the total control cohort (r=0.68, p<0.001), but not the IIH patient cohort (r=-0.35, p=0.12). Similarly, the serum and CSF resistin levels were significantly correlated when the whole cohort was considered (r=0.26, p=0.03), but this was not the case for the IIH patients (r=0.32, p=0.17) or for the control subject cohort (r=0.25, p=0.08).

Further sub analysis was performed by considering the controls according to the four diagnostic groups (MS, CVS, MIX and N). Of all the separate analyses, only CSF IL-8 showed a significant difference, with higher concentrations in the MS cohort (p=0.02). Regression analysis confirmed this to be an effect of disease group as age, gender and BMI did not significantly influence the result. Finally, the data was explored with subjects considered in three groupings, IIH patients, 'disease controls' (MS+CVS+MIX) and patients with normal investigations (N). This did not affect the results significantly, with the exception of serum IL-8 which was identified as being higher amongst disease controls than patients in the IIH and N diagnostic groups.

2.4 Discussion

Profiles of adipokines and inflammatory cytokines have not previously been compared between IIH and other neurological diseases. Although a distinct IIH-specific cytokine profile has not been identified, the adipokine leptin appears to be significantly dysregulated in the CSF of patients with IIH.

A significant elevation of serum leptin levels amongst patients with IIH was found in this study, but this significance was lost when levels were adjusted for age, gender and BMI. Previous studies have reported elevated serum leptin in IIH compared with control groups. (Lampl et al., 2002; Subramanian et al., 2004) However, the two studies concerned did not carry out multivariable regression analysis and the confounding effect of elevated BMI may not have been excluded. The serum leptin results in this study do mirror previous studies documenting sexual dimorphism, with levels higher in women than men, and a positive correlation with age and BMI. (Ostlund et al., 1996; Schwartz et al., 1996; Nam et al., 2001)

It should be noted that subjects were not fasted prior to the collection of blood and CSF samples. Serum leptin levels can reportedly be influenced by fasting, (Weigle et al., 1997) although acute alterations in food intake have been shown not to affect circulating levels. (Korbonits et al., 1997) Data from the study by Wong et al (2004) suggests that there is very little variation in the levels of CSF leptin over a 24 hour period or in response to food intake. It is unlikely that the lack of fasting amongst the patients in this study had a major effect on the results.

An important and novel finding was the elevated CSF leptin in patients with IIH, which remained significantly raised after adjustments for age, gender and BMI. The CSF leptin levels in this study were higher than previously published values, possibly reflecting differences in the recombinant leptin used to standardise the assays. (Caro et al., 1996; Schwartz et al., 1996; Meier and Gressner, 2004; Wong et al., 2004) The use of control subjects from a neurological disease population, where permeability of the blood brain barrier may be affected, may also be relevant. CSF leptin levels vary very little when measured over a 24 hour period, (Wong et al., 2004) but levels can be influenced by drug therapy. (Rodrigues et al., 2002) There were no consistent trends regarding prescribed medication amongst the subjects in this study. Only four patients with IIH were taking acetazolamide and four patients in the whole group were using hormonal contraceptives. Medication use is unlikely to have significantly contributed to the results seen.

CSF leptin was noted to significantly correlate with intracranial pressure, but analysis confined to the IIH cohort failed to identify a linear correlation. This may possibly reflect a more complex relationship between leptin and CSF opening pressure at higher intracranial

pressures. The role of CSF leptin and how it may be involved in intracranial pressure homeostasis or the pathogenesis of IIH remains to be explored.

It is interesting that despite high levels of CSF leptin and the potential for hypothalamic signalling to indicate satiety, IIH patients remain overweight. In obesity, levels of serum leptin are elevated but there is an apparent resistance to its appetite suppressing effects. (Schwartz et al., 1996) This has been postulated to occur as a result of either impaired transport of leptin across the blood-brain-barrier, or impaired leptin signalling at the hypothalamus. (Flier, 2004) In support of the impaired transport theory, CSF:serum leptin ratios are reduced in obesity. (Caro et al., 1996) In addition, infusion of leptin into the CSF of overweight leptin-deficient rats has been shown to cause weight loss. (Van Heek et al., 1997) The elevated CSF leptin seen in our cohort of patients with IIH may suggest that the aetiology of the obesity in IIH is failed leptin signalling at the hypothalamus.

The origin of the CSF leptin in IIH is of interest. This study found that neither CSF nor serum leptin levels correlated with BMI in subjects with IIH, yet both correlated significantly with BMI in the control population. A similar finding was reported by Lampl et al (2002) who showed a significant association of leptin with BMI in the serum of healthy control subjects, including an obese cohort, but not in a cohort of 15 IIH patients. Furthermore, the relationship between serum and CSF leptin in this study was not significant for the IIH patient cohort, ($r=-0.35$, $p=0.12$) but showed a significant positive correlation amongst all patients together ($r=0.66$, $p<0.001$) as well as the control group ($r=0.68$, $p<0.001$). When CSF:serum ratios were compared for all adipokines, no differences were identified between the diagnostic groups. However, CSF:serum leptin ratios showed a trend towards higher values in the IIH cohort (0.61 compared to 0.39 in the control population, $p = 0.075$). These

findings suggest that, in contrast to the situation in normal obese individuals, transfer of leptin across the blood brain barrier in IIH is not impaired and may even be enhanced. Alternatively, up-regulation of leptin secretion from central nervous system locations may explain why CSF leptin levels are significantly elevated in IIH; extra-adipose sites of leptin secretion have been previously documented in the stomach, heart, pituitary and hypothalamus. (Green et al., 1995; Bado et al., 1998; Morash et al., 1999) It remains unclear whether elevated CSF leptin is a cause or a consequence of the pathogenic process underlying IIH.

Obesity was characterised by an inflammatory cytokine profile (CSF IL-6, CSF PAI-1, CSF resistin, CSF leptin and serum leptin) in this neurological patient cohort, although not all the cytokines previously documented in obesity were dysregulated. (Maedler et al., 2002; Straczkowski et al.; 2002, Sartipy and Loskutoff; 2003; Park et al., 2005; Straczkowski et al., 2006) Levels of adiponectin, an adipokine with seemingly antagonistic effects to leptin, were reduced in both the CSF and serum in IIH patients compared to the control group, but this did not reach statistical significance when age and BMI were taken into account. The results did not identify significantly deranged cytokine profiles in IIH patients compared with controls, although IL-8 and MCP-1 were present at higher concentrations in the control group as a whole, a likely effect of the inclusion of control subjects with inflammatory disease. Sub-analysis of the results by individual diagnostic groups did not identify any disease-specific inflammatory cytokine profiles, with the exception of CSF IL-8, which was elevated in the MS cohort, as has been shown by other studies. (Cannella and Raine, 1995; Ishizu et al., 2005) Very little is known about the transfer of certain cytokines across the blood brain barrier and their role in many neurological conditions. Thus, the lack of

significant cytokine abnormalities and specific profiles in this study does not exclude their involvement in the pathogenesis of IIH.

2.5 Summary

No previous studies have characterised cytokine levels in the serum and CSF of patients with IIH. The findings of this study appear to indicate that IIH is not an inflammatory condition as may have been predicted from the associated obesity phenotype. A novel finding of significantly elevated CSF leptin in IIH has been demonstrated, independent of BMI. Additionally levels of CSF leptin positively correlate with intracranial pressure in control subjects but not in patients with IIH. These findings suggest that failure of leptin signalling at the hypothalamus may be important in the pathophysiology of the obesity seen in patients with IIH. In addition, increased CSF leptin may be important in the underlying pathogenic processes that lead to the development of IIH. Further study of the central actions of leptin and its possible role in the regulation of intracranial pressure and satiety may shed light on the mechanisms underlying IIH.

CHAPTER 3 THE IIH TRIAL PILOT

A PRAGMATIC RANDOMISED CONTROLLED TRIAL OF TREATMENT FOR IDIOPATHIC INTRACRANIAL HYPERTENSION

3.1 Background

Evidence of the effectiveness of treatments for IIH is poor, with most of the data coming from small retrospective case series. Even the largest prospective studies have involved only 35, (Rowe and Sarkies, 1998) 50 (Wall and George, 1991) and 81 patients. (Radhakrishnan et al., 1993) A Cochrane systematic review in 2005 failed to find a randomised controlled trial of any treatment option in this disease area. (Lueck and McIlwaine, 2005) Acetazolamide is a widely used treatment, but with the exception of one small study, (Celebisoy et al., 2007) has not been formally evaluated in IIH. There is increasing belief that weight reduction is beneficial and possibly even curative, but this too needs further investigation. Thus, controversies abound in the management of IIH and there is an urgent need for well designed clinical trials.

Similarly, there is no consensus regarding the best way to monitor patients with IIH. There are uncertainties surrounding the natural history of the condition and the identification of those most at risk of visual loss. In clinical practice, routine reviews tend to combine the assessment of symptoms with ophthalmological examination and measurement of visual function, giving an overview of the patient's presentation. Assessments of disease status are subjective and no agreed grades of IIH severity exist. There are no specific criteria to guide the clinical decision-making and the timing of any intervention is left to the judgement of the

treating clinician. Even the concept of 'cure' in IIH is fraught with difficulty. Resolution of all symptoms and abnormal signs indicates remission of the condition, but in many instances, headache or minor changes in the appearance of the optic discs or visual fields can persist, suggesting the presence of residual disease. It can be difficult to ascertain whether a patient's discs have returned to normal or to be certain that a patient's headache is actually due to raised intracranial pressure. Thus whilst a definition of cure may be straightforward and easily agreed, applying that definition to a particular patient can be problematic.

Clinical experience suggests that several factors are considered in deciding whether a patient with IIH is improving or deteriorating. A variable combination of symptoms, signs and visual parameters appears to dictate the management strategy. Some studies have highlighted the relative importance of visual field assessment in predicting outcome (Wall and George, 1991; Rowe and Sarkies, 1998) and this is often reflected in current practice, but treatment is also guided, to a greater or lesser degree, by presenting symptoms, papilloedema and performance on other tests of vision. Studies in IIH must acknowledge this multi-factorial approach to disease evaluation. Striving towards a single measure of outcome in IIH may be futile; instead a composite outcome may perform better as a measure of disease status and warrants further study.

Since so little is known about the effects of different treatments and the most appropriate outcome measures in IIH, large scale clinical trials cannot be properly planned. A pilot study is required to explore the feasibility of such trials as well as provide data to inform sample size and power calculations in their design.

3.1.1 Objectives

This pilot study was designed to prospectively evaluate a cohort of newly diagnosed patients with IIH, with the following aims:

- To examine the feasibility of a randomised controlled trial of treatment for IIH
- To obtain data upon which to base future calculations of sample size and anticipated treatment effect for a large scale trial
- To observe the use of acetazolamide and its effect upon various measures of disease status in IIH
- To observe the effects of weight reduction in patients who were overweight, by comparing outcomes between those who did and those who did not lose weight
- To explore the commonly employed measures of disease status in IIH and identify features of the clinical assessment that most influenced the overall status of patients with IIH

3.2 Methods

3.2.1 Trial Design

A pragmatic trial design was adopted for this study. An open-label, prospective, randomised controlled structure was chosen to complement normal clinical practice and maximise recruitment. Patients and treating clinicians were not blinded to the treatment allocation.

Patients presenting to the neurology and ophthalmology units of the participating hospitals who met the inclusion criteria were informed of the study by their treating clinician and

invited to take part. They were provided with an information sheet and asked to give written informed consent for the study.

Randomisation was performed by the University of Birmingham Clinical Trials Unit, via a telephone call from the treating clinician, once consent had been obtained. Allocation was determined by a computer-generated random list. Patients were randomised to receive either treatment with acetazolamide or no acetazolamide. Randomisation was based upon the uncertainty principle; if the supervising clinician believed that a patient should definitely receive or not receive treatment with acetazolamide, the patient was not eligible for inclusion in the study.

Acetazolamide was used within licence, according to the Summary of Product Characteristics (SPC). The dosing schedule was left to the discretion of the treating clinician, in accordance with their normal clinical practice. Regardless of treatment allocation, all overweight patients were advised to follow a weight reduction programme. Overweight patients were referred for assistance with weight reduction, such as advice from a dietician, in keeping with the normal policy of the treating centre.

It was anticipated that some patients would deteriorate regardless of initial treatment. Supervising clinicians were advised to use their normal judgement to decide if and when patients should receive additional intervention. The supervising clinician was able to initiate changes to the dosing schedule of acetazolamide in those patients randomised to receive it and to commence treatment with acetazolamide in patients allocated not to receive it. The decision to refer patients for further or urgent intervention, such as surgery, was also left to the discretion of the treating clinician.

The duration of the study period was 12 months from randomisation. Data was collected at baseline and at 3, 6, 9 and 12-months, totalling five visits. It was customary for some centres to schedule reviews at additional time points within the one year period; where this was the case, abbreviated data was collected as "additional visit" information. Data was recorded on visit-specific forms, provided as a trial pack for each patient (see Appendix 1) Various measures were documented by the treating clinician at each visit, with patient questionnaires completed at visits 1 (baseline), 3 (6 months) and 5 (12 months). All of the documented information from a single visit was returned by post to the trial coordinator for entry onto the trial database.

Approval for the study was granted by the North West Multicentre Regional Ethics Committee. The Medicines and Healthcare products Regulatory Authority (MHRA) approved the use of acetazolamide in this trial. The trial was registered with the European Clinical Trials Database (European Union Drug Regulating Authorities Clinical Trials, EudraCT number 2004-001595-40).

3.2.2 Trial Centres

Patients were recruited from six neurology and ophthalmology units in the Midlands area of the UK. The main trial centre was in Birmingham, within the Neurology department of City Hospital (Sandwell and West Birmingham NHS Trust) and the adjoining Birmingham and Midland Eye Centre, which is a regional tertiary referral centre for neuro-ophthalmology in the West Midlands. Additional sites were identified by the Trial Steering Committee and chosen on the basis of availability of interested senior clinicians, appropriate facilities and local neuro-ophthalmology expertise.

Site-specific local research ethics committee approval was granted for the following additional centres:

- University Hospital Birmingham NHS Foundation Trust
- Royal Wolverhampton Hospitals NHS Trust
- University Hospitals Leicester NHS Trust
- Sheffield Teaching Hospitals NHS Foundation Trust
- United Lincolnshire Hospitals NHS Trust
- University Hospital North Staffordshire NHS Trust

All sites were coordinated through the main trial centre and the same trial manager performed the site visits, training and data entry for all of the centres.

3.2.3 Patients

Clinical audit in 2004 showed that approximately 50 cases of IIH present to the Birmingham and Midland Eye Centre and the neurology and ophthalmology services of City Hospital and University Hospital each year. By increasing the area covered by the pilot study to the above centres, it was anticipated that 50 patients could be recruited in a 12-month period.

3.2.3.1 Inclusion Criteria

- New diagnosis of IIH according to modern criteria (Friedman and Jacobson, 2002)
- Normal imaging (cerebral MRI and MR venogram or CT venogram normal)
- Documented elevation of CSF opening pressure above 25cm at lumbar puncture
- Normal CSF constituents
- Normal routine haematology and biochemistry (no abnormalities of full blood count or urea and electrolytes)
- Willing and able to give written informed consent
- Able to complete trial documentation
- Randomising clinician uncertain about the treatment the patient should receive

3.2.3.2 Exclusion Criteria

- Intracranial hypertension due to cerebral venous sinus thrombosis, structural, metabolic or other cause
- Contraindication to acetazolamide: hypokalaemia, hyponatraemia, metabolic acidosis, severe hepatic or renal impairment, sulphonamide sensitivity
- Pregnancy or planned pregnancy
- Randomising clinician certain about the treatment the patient should receive

3.2.4 Outcome Measures

No single or main outcome could be chosen, since a principal aim of this pilot was to explore a variety of measures of IIH status. The data collected can be summarised as:

1. Demographic data
2. Pragmatic outcome measures
    a. Presence or absence of symptoms
    b. Headache visual analogue score (VAS)
    c. Intervention
        i. Changes to acetazolamide
        ii. Surgery
3. Visual Function
    a. Acuity
    b. Visual Field
    c. Contrast Sensitivity
    d. Optic disc appearance
4. Health related quality of life / mood
    a. Short Form 36
    b. Hospital Anxiety and Depression Score
    c. EuroQoL EQ-5D

In addition, serious unexpected suspected adverse reactions (SUSARS) were monitored throughout the trial.

3.2.4.1 Demographic data

The following data were recorded at baseline:

- Hospital identification number and recruiting centre
- Date of birth, ethnic group
- Height (metres) and weight (kilograms; to nearest 0.5kg)
- Any pre-existing neurological or ocular disease
- Current medication
- Prior use of antibiotics (in previous 6 months), hormonal medication, lithium or vitamin A or its derivatives
- Any other relevant medical or surgical history
- Documented CSF opening pressure in cm

3.2.4.1 Pragmatic outcome measures

3.2.4.1.1 Symptoms

At baseline, as well as at each subsequent visit, patients were asked about the presence or absence of the following symptoms:

- headache
- tinnitus
- visual loss
- transient visual obscurations
- diplopia
- any other symptom

Space was provided for the assessing clinician to elaborate on any of the items using free text entries. Headache was rated on a 10 point scale by the patient. They were asked to choose a score from 1 to 10 to describe their current headache, with 1 indicating no headache and 10 being the worst headache imaginable.

3.2.4.1.2 Intervention: Acetazolamide

A series of questions relating to the treatment allocation was included at each visit.

- For the acetazolamide group the questions were:
  1. Is the patient still taking acetazolamide?
  2. Current dose of acetazolamide

3. Has the dose been changed?
4. Reason for dose change (if known)
5. Reason(s) for stopping acetazolamide from a choice of any or all of:
    a. Adverse effects of medication
    b. Patient preference
    c. Pregnancy or planned pregnancy
    d. Other reason

- For the control group the questions were:
    1. Has acetazolamide been added?
    2. Date commenced acetazolamide (if applicable)
    3. Current dose (if applicable)
    4. Reasons for adding acetazolamide from a choice of any or all of:
        a. Worsening visual field
        b. Worsened disc appearance
        c. Reduced acuity
        d. Development of afferent pupillary defect
        e. Headaches failing to resolve
        f. New visual obscurations
        g. Worsening tinnitus
        h. Worsening impairment of colour vision
        i. Other

3.2.4.1.3 Intervention: Surgery

At each visit, clinicians were asked whether surgery was indicated for the patient and if so, to document the reason for surgery. Space for free text was provided on the forms.

3.2.4.2 Visual Function measures

3.2.4.2.1 Visual acuity

Visual acuity was measured at each visit after refraction on standard LogMAR charts (Figure 3.1) with uniform illumination at a distance of 4 metres. LogMAR is the logarithm of the minimum angle of resolution (MAR). Two charts are available, the Bailey-Lovie and the

Lighthouse charts. (Holladay and Prager, 1989) The MAR relates to the resolution required to resolve the elements of a letter. (Bailey and Lovie, 1976) Thus Snellen acuity 6/6 equates to a MAR of one minute of arc, 6/12 equates to two minutes of arc and so on. LogMAR is the Log_{10} of the MAR (See table 3.1). Snellen charts have irregular progression of letter size, variation in number of letters per line, difference in legibility of letters and the spaces between letters and rows have no relationship. In contrast, LogMAR charts have logarithmic progression in letter and row size, equal numbers of letters per line and letters of equal legibility. Therefore the only parameter likely to influence visual acuity levels is the letter size. (Bailey and Lovie, 1980) Each letter on a line is equal to log 0.02. If the patient is unable to read the whole line, 0.02 for each letter on the line read correctly is subtracted from the value of the last whole line read, for values below 0.0, or added, for values better than 0.0. A lower number equates to a better visual acuity.

Table 3.1 Snellen to LogMAR comparisons

Snellen	LogMAR
6/120	1.3
6/60	1.0
6/24	0.6
6/9.5	0.2
6/6	0.0
6/4.8	-0.1

Figure 3.1 LogMAR acuity chart

3.2.4.2.2 Visual fields

Visual fields were recorded at each visit. Humphrey automated perimetry was used. The programme used was a central 24-2 SITA test (Swedish Interactive Threshold Algorithm) with Statpac software. Visual thresholds were established at loci separated by six degrees throughout the central 24 degrees of the visual field. The starting stimulus light intensity was 6 dB brighter than the age-matched standard for each location and the stimulus had duration of 0.02 seconds. The 24-2 programme was chosen as it is most commonly used in the assessment of optic nerve disease and was available at all trial centres. In addition, effective screening is achieved with minimal testing time and patient fatigue.

The mean deviation (MD) value, a measure of the average amount by which the measured threshold differed from the age corrected normal, was recorded in decibels. In addition, the pattern standard deviation, a measure of localised non-uniformity, was recorded. If any of the global incides fell outside the expected range of normal, they were flagged with a p

value. The numbers of fixation losses were recorded as well as the percentages of false positive and false negative errors, so that unreliable recordings could be excluded from later analysis.

3.2.4.2.3 Contrast Sensitivity

Where available, contrast sensitivity was assessed for both eyes individually, as well as for binocular vision, using a Pelli-Robson chart under standard illumination. Patients were tested three times, each eye separately and both eyes together, wearing their normal distance correction, if any.

Scoring grids were provided, so that the log contrast sensitivity for the faintest triplet for which two of the three letters were named correctly could be recorded. (Figure 3.2) The log contrast sensitivity is given by the number on the grid nearest to the letter triplet. Two different sets of letter sequences were available on charts which were otherwise identical, to vary the letters in case patients had memorised them. Patients were encouraged not to give up too soon and to make a guess even when they believed the letters to be invisible. The reliability of the results was dependent upon the allowing sufficient time and only stopping the test once the patient had guessed incorrectly two of the three letters in a triplet. (Pelli et al., 1988)

LEFT EYE				RIGHT EYE				BINOCULAR			
0.00	H S N	D S N	0.15	0.00	H S N	D S N	0.15	0.00	H S N	D S N	0.15
0.30	C K R	Z V R	0.45	0.30	C K R	Z V R	0.45	0.30	C K R	Z V R	0.45
0.60	N D C	O S K	0.75	0.60	N D C	O S K	0.75	0.60	N D C	O S K	0.75
0.90	O Z K	V H Z	1.05	0.90	O Z K	V H Z	1.05	0.90	O Z K	V H Z	1.05
1.20	N H O	N R D	1.35	1.20	N H O	N R D	1.35	1.20	N H O	N R D	1.35
1.50	V R C	O V H	1.65	1.50	V R C	O V H	1.65	1.50	V R C	O V H	1.65
1.80	C D S	N D C	1.95	1.80	C D S	N D C	1.95	1.80	C D S	N D C	1.95
2.10	K V C	O H R	2.25	2.10	K V Z	O H R	2.25	2.10	K V Z	O H R	2.25

Figure 3.2: Scoring grids for Pelli-Robson Contrast Sensitivity.

3.2.4.2.4 Papilloedema

Papilloedema was documented as present or absent for each eye by the examining clinician. Photographs of both optic discs were taken with pupils dilated using a Topcon Trc 50IX© digital fundus camera (Topcon Corporation, Japan). Clinicians were not asked to assign a grade to or comment on the severity of the disc appearances. Digital images were stored for use in a later study (see Chapter 4).

3.2.4.3 Health related quality of life and depression

All patients were asked to complete a questionnaire at baseline, 6 months and 12 months, comprising three validated measures. (Appendix 2)

3.2.4.3.1 Short Form 36 (SF36)

The multi-purpose Short Form 36® health survey is a generic measure used in surveys of general and specific populations, comparing the relative burden of diseases and differentiating the health benefits produced by different treatments. Comprising 36 questions, it yields an eight scale profile of functional health and well-being as well as psychometrically-based physical and mental health summary measures. The following eight health concepts are measured, which are relevant across age, disease and treatment groups: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional problems and mental health (psychological distress and psychological well being). The survey uses a standardized scoring system, producing two summary measures and a self-evaluated change in health status in addition to the eight health scores. Higher scores are indicative of more positive quality of life.

3.2.4.3.2 Hospital Anxiety and Depression Scale (HADS)

Psychological well-being was assessed by the Hospital Anxiety and Depression Scale (HADS). (Zigmond and Snaith, 1983) This is a brief self-report measure that provides two separate scores for anxiety and depression. It was designed to assess milder forms of mood disorder in non-psychiatric hospital outpatients. Scores range from 0 to 21, with higher scores indicative of more anxiety and greater depression. Score of 0-7 is in the normal range, 8-10 borderline and 11-21 is the abnormal range.

3.2.4.3.3 The EuroQoL EQ-5D

Patient rated health status was assessed using EuroQoL EQ-5D (©1990 EuroQol Group), a standardised instrument measuring health outcome. Applicable to a wide range of health conditions it provides a descriptive profile (i) and single index (ii) for health status. It was designed as a simple generic measure of health for clinical and economical appraisal.(Brooks et al., 2003)

(i) The EQ-5D descriptive system has five dimensions: mobility, self care, usual activities, pain/ discomfort and anxiety / depression. There are three levels for each dimension: no problems, some problems, severe problems. Health states are then referred to in 5-digit code, where '11111' represents no problems and '33333' represents severe problems in all dimensions. Weights are used to score the responses to the 5 domains, with scores ranging from 0 to 1 (where a score of 1 represents a perfect state). Utilities or societal valuations placed on each state are based on a UK sample of 3,235 persons using time trade off to determine valuations. (Dolan et al., 1995)

(ii)The EQ-VAS (visual analogue score) is from 0 (worst) to 100 (best). Respondents rate their own health on a vertical 'thermometer' scale labelled 'best imaginable health state' and 'worst imaginable health state'.

3.2.4.4 Composite Outcome Measures

3.2.4.4.1 Final Status Score

At the final (12-month) visit, treating clinicians were asked to describe each of the patient's headache, tinnitus and visual obscurations as absent (0 points), present, - stable (1 point) or deteriorating (2 points), along with visual acuity, visual field and optic disc appearance as normal (0 points), abnormal, - stable (1 point) or deteriorating (2 points). Summation of each item produced a Final Status Score ranging from 0 for the best outcome to 12 for the worst (Table 3.2)

3.2.4.4.2 Final Outcome

Also at the 12-month visit, clinicians were asked to choose which term best described the patient's IIH at that visit, from a choice of four:

1. IIH in remission
2. Active IIH improving
3. Active IIH but stable
4. Active IIH deteriorating

Table 3.2: Scoring system for IIH Final Status Score

Item	Description	Select one (✓)	Score
1. Headache	Absent	[ ]	0
	Present, stable	[ ]	1
	Deteriorating	[ ]	2
2. Tinnitus	Absent	[ ]	0
	Present, stable	[ ]	1
	Deteriorating	[ ]	2
3. Visual obscurations	Absent	[ ]	0
	Abnormal, stable	[ ]	1
	Deteriorating	[ ]	2
4. Visual Acuity	Normal	[ ]	0
	Abnormal, stable	[ ]	1
	Deteriorating	[ ]	2
5. Optic Disc	Normal	[ ]	0
	Abnormal, stable	[ ]	1
	Deteriorating	[ ]	2
6. Visual Field	Normal	[ ]	0
	Abnormal, stable	[ ]	1
	Deteriorating	[ ]	2
	Total maximum score:		*12*

3.2.5 Statistical analysis

Statistical analyses were performed using SAS (Statistical Analysis Software, SAS Institute Inc.,Cary, NC) and SPSS 17.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL.) Graphs were produced using Microsoft Excel 2007 and GraphPad Prism 5 (GraphPad Software Inc., La Jolla, Ca.)

Being a feasibility study, the trial was not powered to provide definitive efficacy results. Intention-to-treat point estimates and confidence intervals (CI) were calculated for clinical outcomes. Differences between dichotomous variables were analysed as Peto odds ratios to examine treatment effect; for continuous variables, the mean values were compared. Repeated measures analysis was applied to longitudinal data. Continuous and ordinal non-parametric variables were compared between groups using the Mann-Whitney *U* test, or Cuzick's test for trend if they were measured across three or more ordered groups. The tests were two-tailed with significance set at 5%. Association between categorical variables was measured using Somers' D, an asymmetric measure of the effect of a given predictor variable on outcome.

3.3 Results

3.3.1 Recruitment

The first of a total of 50 patients was recruited in February 2005 and the last, in December 2006. Five of the approved centres recruited patients to the trial: The Birmingham and Midland Eye Centre (Sandwell and West Birmingham NHS Trust), Leicester Royal Infirmary, Sheffield Teaching Hospitals NHS Trust (Royal Hallamshire Hospital), University Hospital of North Staffordshire, (Stoke on Trent) and United Lincolnshire Hospitals NHS Trust.

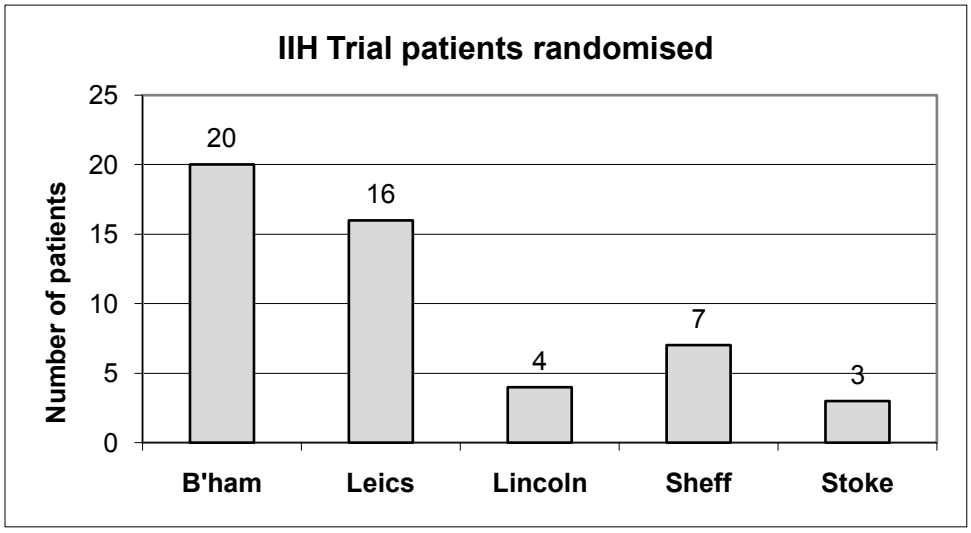


Figure 3.3: Total numbers of patients recruited by each centre in the IIH Trial

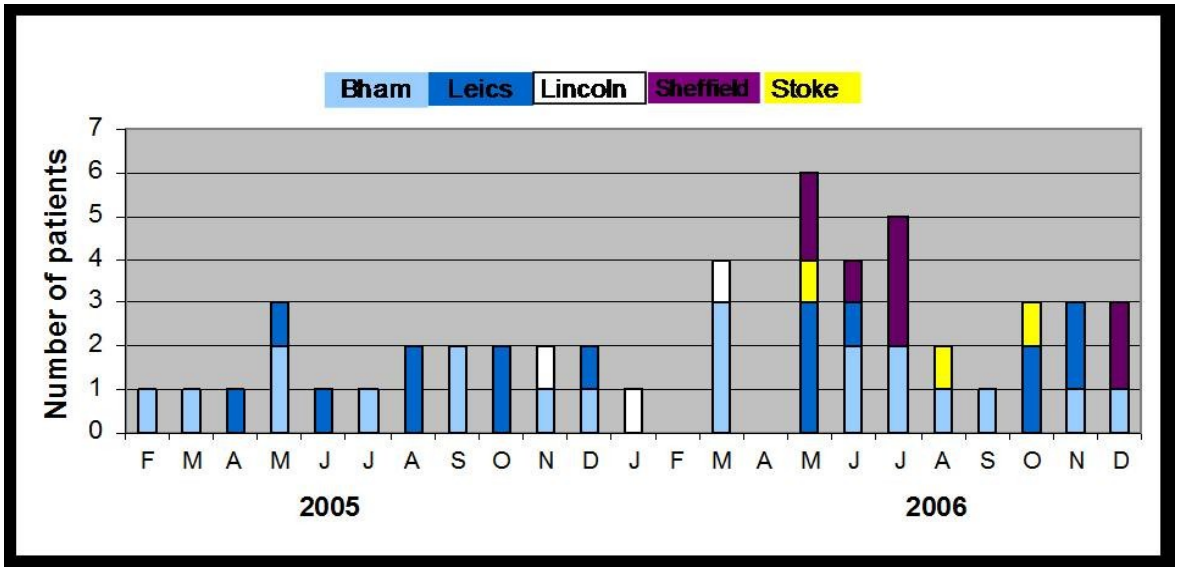


Figure 3.4: Patients randomised, by centre, during each month of the total recruitment period

3.3.2 Ineligible patients

For the Birmingham centre only, data was available for all patients screened for inclusion. From a total of 84 patients screened, 34 were ineligible for a variety of reasons (table 3.3) In the majority of cases, patients were ineligible because they had been prescribed acetazolamide during their acute hospital admission, immediately following the diagnostic lumbar puncture and prior to neuro-ophthalmology assessment and invitation to the trial.

Amongst the six patients who declined consent, three expressed concern about the concept of randomisation, two indicating a strong preference for receiving medication and one preferring not to receive any. One of the other three patients had concerns about travel to appointments in Birmingham; the other two did not cite specific reasons.

Table 3.3 Reasons for ineligibility of screened patients

Acetazolamide already commenced	9
Declined consent	7
Anaemia	5
Referred for surgery	3
Acetazolamide contraindicated	3
Absent papilloedema	3
CSF abnormalities	2
Unable to give consent	1
Borderline CSF pressure	1
Total	*34*

Four women and one man were found to be anaemic during screening. The haemoglobin values ranged from 5.5gdl^{-1} to 9.0 gdl^{-1} amongst the women (normal range 11.5 to 16.0gdl^{-1}); in the male patient it was 9.2gdl^{-1} (Normal range 13.5 to 18.0gdl^{-1}). As discussed in chapter one, all patients had a microcytic blood picture and all had improvement of their intracranial hypertension symptoms when the anaemia was treated.

Three patients presented with visual loss and clinical findings that were felt to warrant immediate surgical intervention. All three underwent insertion of lumboperitoneal (LP) or ventriculoperitoneal (VP) shunt in the neurosurgical unit, within five days of their initial presentation.

Acetazolamide was contraindicated in two patients, one due to current pregnancy and one, planned pregnancy. A third patient was assessed by the treating clinician as having disease

which definitely did not require drug treatment, hence was ineligible according to the uncertainty principle.

Three patients appeared to have papilloedema upon initial presentation, which led to a series of investigations for IIH, but were subsequently found not to have papilloedema when neuro-ophthalmology review including slit lamp examination was carried out. One of the patients was found to have optic nerve head drusen, with a similar appearance to papilloedema. Although this patient had an opening CSF pressure of 34cm, there were no symptoms or signs of raised intracranial pressure, the patient having undergone investigations due to the appearance at fundoscopy of their optic discs. No diagnosis of IIH was made and the patient was simply kept under review. In the case of the other two patients, in whom the optic discs appeared normal, no consensus of opinion about the diagnosis could be reached.

Two patients were found to have CSF pleocytosis which precluded the diagnosis of IIH and were referred for further investigation. One patient had a CSF opening pressure of 21cm and was excluded. One patient had learning difficulties and was unable to give informed consent.

3.3.3. Demographics

50 patients fulfilled the inclusion criteria for inclusion and were recruited. The characteristics of these patients are shown in table 3.4. There were 25 patients in each randomisation arm. Overall, 46 patients were female and the mean age was 31 years (range 18 to 66 years). The recorded opening pressure at diagnostic lumbar puncture ranged from 25.0 to 78.0cm. Baseline weight amongst the 50 patients ranged from 72.5 to 146.0 kg, with corresponding values of body mass index (BMI) from 23.7 to 60.6 kgm^{-2}. As expected there were no

significant differences between the allocation arms; the Mann Whitney two-tailed p values for age, BMI and CSF pressure were p = 0.57, 0.12 and 0.66 respectively (figure 3.5.)

Table 3.4 Characteristics of patients by allocation. Medians and ranges are given. OP = opening pressure at diagnostic lumbar puncture

	Acetazolamide	*No Acetazolamide*
N	25	25
Age	29 (18-66)	33 (18-63)
F:M	22:3	24:1
CSF OP cm	38.5 (26.5-51.0)	39.0 (25.0-78.0)
BMI kgm^{-2}	38.4 (29.8-60.6)	34.1 (23.7-48.8)

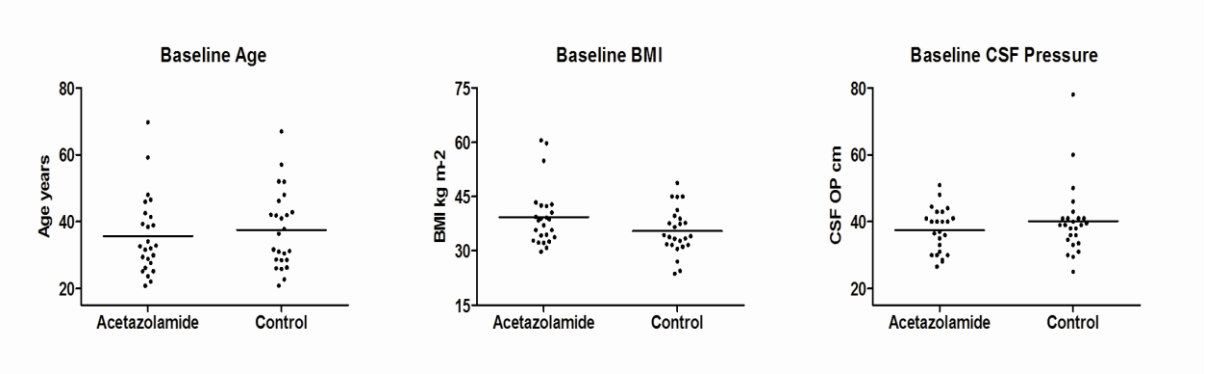


Figure 3.5 Baseline demographics by allocation

Ethnicity was recorded as White British in 40 of the 50 patients (80%), Black Caribbean in five (10%), Indian in three, Pakistani in one and White Irish in one patient.

3.3.3.1 Medical History

Two patients had prior ocular conditions; one had recurrent IIH, having being diagnosed and treated 20 years previously, the other right sided amblyopia diagnosed aged 3 years. Four patients reported a history of migraine. One patient had a history of Bell's palsy in childhood; no other prior neurological conditions were reported.

Systemic arterial hypertension was recorded in 8 patients (16%), two male and six female. The male patients were 52 and 70 years, the age range in the females was 29 -67, mean 46 years. Two patients had a history of depression, one with associated panic disorder.

Three patients reported menstrual dysfunction. One patient was being investigated for polycystic ovary syndrome for oligomenorrhoea, one reported 'erratic' menstrual periods and one patient had a combination of oligomenorrhoea and menorrhagia. One further patient had undergone a hysterectomy two years prior to recruitment.

A variety of prior medical or surgical diagnoses were reported for individual patients, as shown in table 3.5.

Table 3.5 Prior medical or surgical diagnoses

Condition	**Number of patients**	***%***
Hypertension	8	*16*
Depression	2	*4*
Migraine	4	*8*
Menstrual dysfunction	3	*6*
Folate deficiency	2	*4*
Osteoarthritis	2	*4*
Gallstones	1	*2*
Eczema	1	*2*
Ulcerative colitis	1	*2*
HIV seropositivity	1	*2*
Obstructive sleep apnoea	1	*2*
Prior hysterectomy	1	*2*
Prior spinal tuberculosis	1	*2*
Prior varicose vein surgery	1	*2*

3.3.3.2 Medication

Prescribed medication other than simple analgesia was recorded in 18 subjects (Table 3.6). Six women were taking an oral contraceptive pill, progestogen-only in three, combined in three. Three further patients had progestogen contraception via subdermal implants and

three were taking oestrogen hormone replacement therapy (HRT). In addition, four women had recently discontinued oral contraceptive medication; in three cases, within eight weeks of recruitment and in once case, six months previously.

Four patients were taking antihypertensive medication and one other person was receiving propranolol as migraine prophylaxis. Three patients were using antidepressants or mood stabilisers, one patient was taking warfarin for familial protein C deficiency, one hypertensive patient was on low-dose aspirin and one patient was on a proton pump inhibitor for dyspepsia. One patient had been prescribed latanoprost eye drops following an isolated finding of raised intraocular pressure prior to the trial; glaucoma was subsequently excluded and the drops discontinued.

Table 3.6 Prescribed medications at baseline

Medication	**Number of patients**	***%***
Oral contraceptive pill	6	*12*
Etonogestrel contraceptive implant	3	*6*
Oestrogen hormone replacement therapy	3	*6*
Antihypertensives	4	*8*
(Labetolol	1	
Amlodipine	1	
Felodipine	1	
Bendrofluazide	1)	
Psychiatric medication	3	*6*
(Citalopram	1	
Paroxetine	1	
Quetiapine	1)	
Folic acid	1	*2*
Propranolol	1	*2*
Omeprazole	1	*2*
Warfarin	1	*2*
Aspirin	1	*2*
Latanoprost eye drops	1	*2*
Topical hydrocortisone	1	*2*

On specific questioning, six patients reported receiving antibiotics during the six months prior to recruitment, amoxycillin in three cases, metronidazole, trimethoprim, erythromycin

in the other three. No patients admitted ingestion of high doses of Vitamin A and none had received lithium.

3.3.4 Clinical Features

3.3.4.1 Symptoms

Table 3.7 shows the prevalence of symptoms. Headache was present in 35 of the 50 patients. A pain score was documented in 44 of the 50 patients, ranging from 1 (15 patients) to 10 (two patients), median score 3. Baseline scores amongst the allocation arms are shown in figure 3.6. In five patients, comment was made that the severity or frequency of headache had lessened following the diagnostic lumbar puncture and in a further three that it had resolved completely. Descriptions were provided in 14 cases, with five headaches described as worse on lying down or waking, four as generalised, throbbing and four as constant.

Table 3.7 Baseline symptoms amongst the 50 patients

Symptom	Prevalence %
Headache	70
Transient Visual Obscurations	64
Tinnitus	56
Diplopia	22
Visual Loss	26
Other	34
Other symptoms	**%**
Nausea	10
Neck pain / stiffness	6
Dizziness / vertigo	6
Photopsia	4
Photophobia	4
Ocular pain	2
Facial numbness	2
Forgetfulness	2

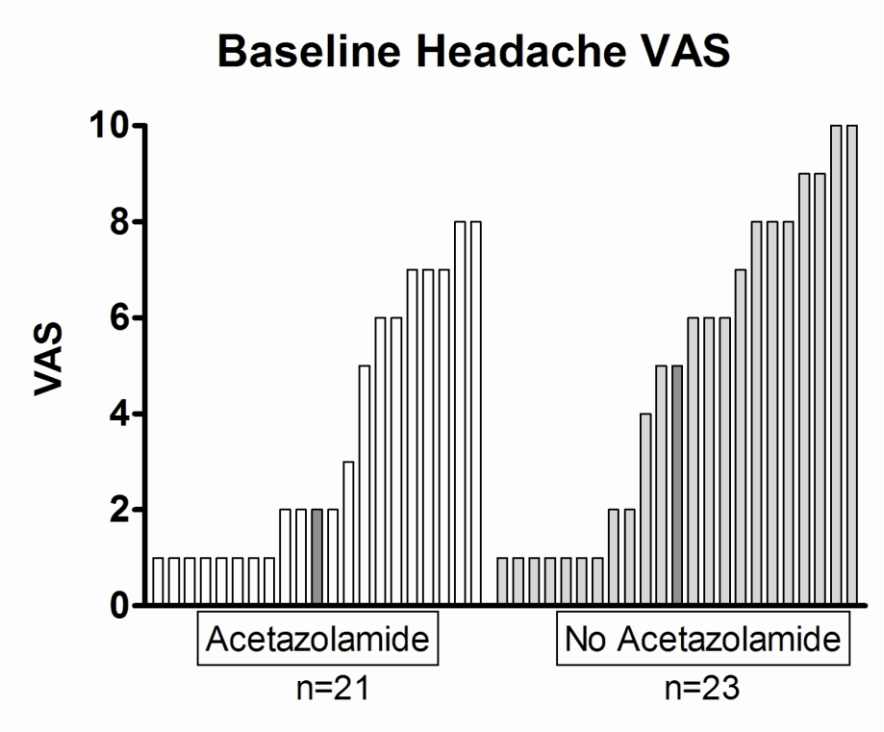


Figure 3.6 Baseline headache visual analogue score (VAS) by allocation. Median values are indicated by shaded bars for the two groups (acetazolamide = 2, control = 5.) There was no difference between the two groups (p=0.21)

Amongst the 32 patients for whom transient visual obscurations were recorded, the symptom was unilateral or highly asymmetrical in 17, described as blurring, clouding and black spots where stated and had an effect of postural change noted in six cases. Of the 26 patients with tinnitus, it was bilateral in nine, unilateral or highly asymmetric in nine and not stated in seven. The descriptions “whooshing”, “roaring”, “pulsatile”, “thumping” and “mechanical” were volunteered in 11 cases. Additional comments were provided for 10 of the 11 patients with diplopia; it was recorded as intermittent in seven and horizontal in five. Comment on visual loss was recorded in 12 of the 13 patients for whom it was reported as a symptom, with visual blurring as the complaint in five.

One patient had no symptoms at all at baseline. One patient had only tinnitus and one patient had only blurred vision. There were two patients whose only symptom was headache and four patients with obscurations as their only symptom.

3.3.4.2 Visual Function

The visual function amongst the 50 patients at baseline is shown in table 3.8 and figures 3.7 and 3.8. All of the 50 patients had papilloedema, which was unilateral in two cases and highly asymmetric in a third. A left sided relative afferent papillary defect was documented in one patient. Four patients were reported to have low test reliability on perimetry and their MD and PSD values were excluded from the analysis.

Table 3.8 Baseline visual function. Medians and ranges are given. MD = mean deviation, PSD = pattern standard deviation (Humphrey automated perimetry)

Papilloedema %	100
Afferent pupillary defect %	2
Left LogMAR acuity	0.0 (-0.20 to 0.40)
Right LogMAR acuity	0.0 (-0.20 to 0.36)
Left MD	-2.19 (-21.15 to 0.94)
Right MD	-2.05 (-17.06 to 0.75)
Left PSD	2.35 (1.07 to 9.68)
Right PSD	2.11 (1.22 to 8.92)
Left contrast sensitivity	1.65 (1.20 to 1.80)
Right contrast sensitivity	1.65 (1.05 to 1.95)
Bilateral contrast sensitivity	1.80 (1.20 to 1.95)

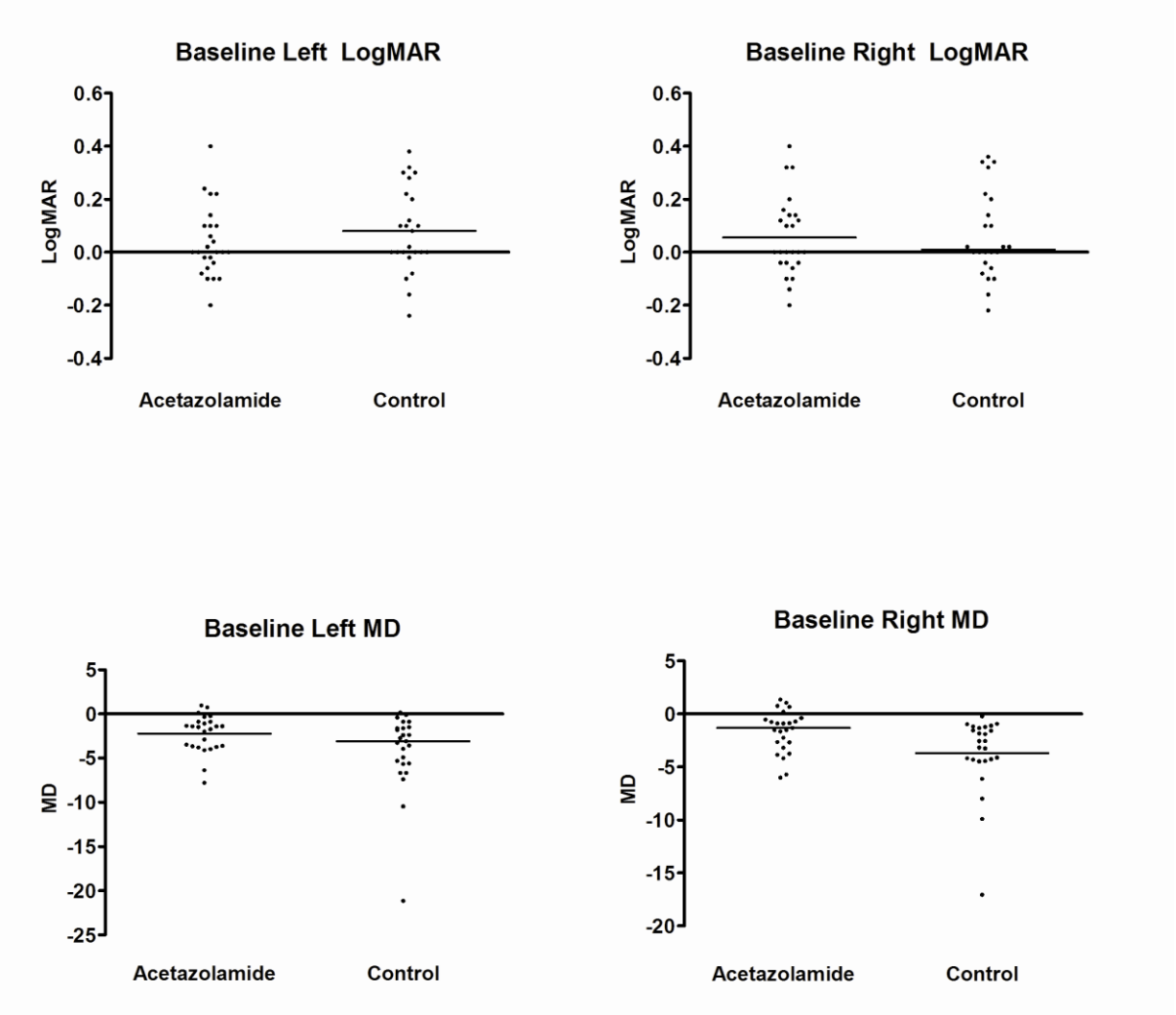


Figure 3.7 Baseline LogMAR acuity and Humphrey perimetry MD values, by allocation. Lines show median values. There were no significant differences between the groups.

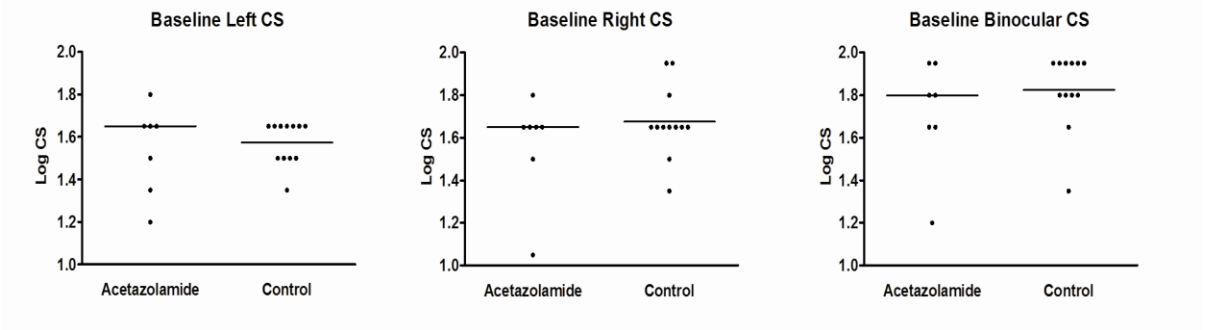


Figure 3.8 Contrast sensitivity by allocation amongst the 19 patients tested

3.3.5 Protocol Compliance

Progression of the 50 patients through the trial is shown in figure 3.9. Final visit data and IIH status was available for 40 patients (80%). 26 patients (52%) attended all five visits and 47 (94%) attended three or more visits. Only one patient dropped out of the study after the baseline visit and was lost to all follow-up.

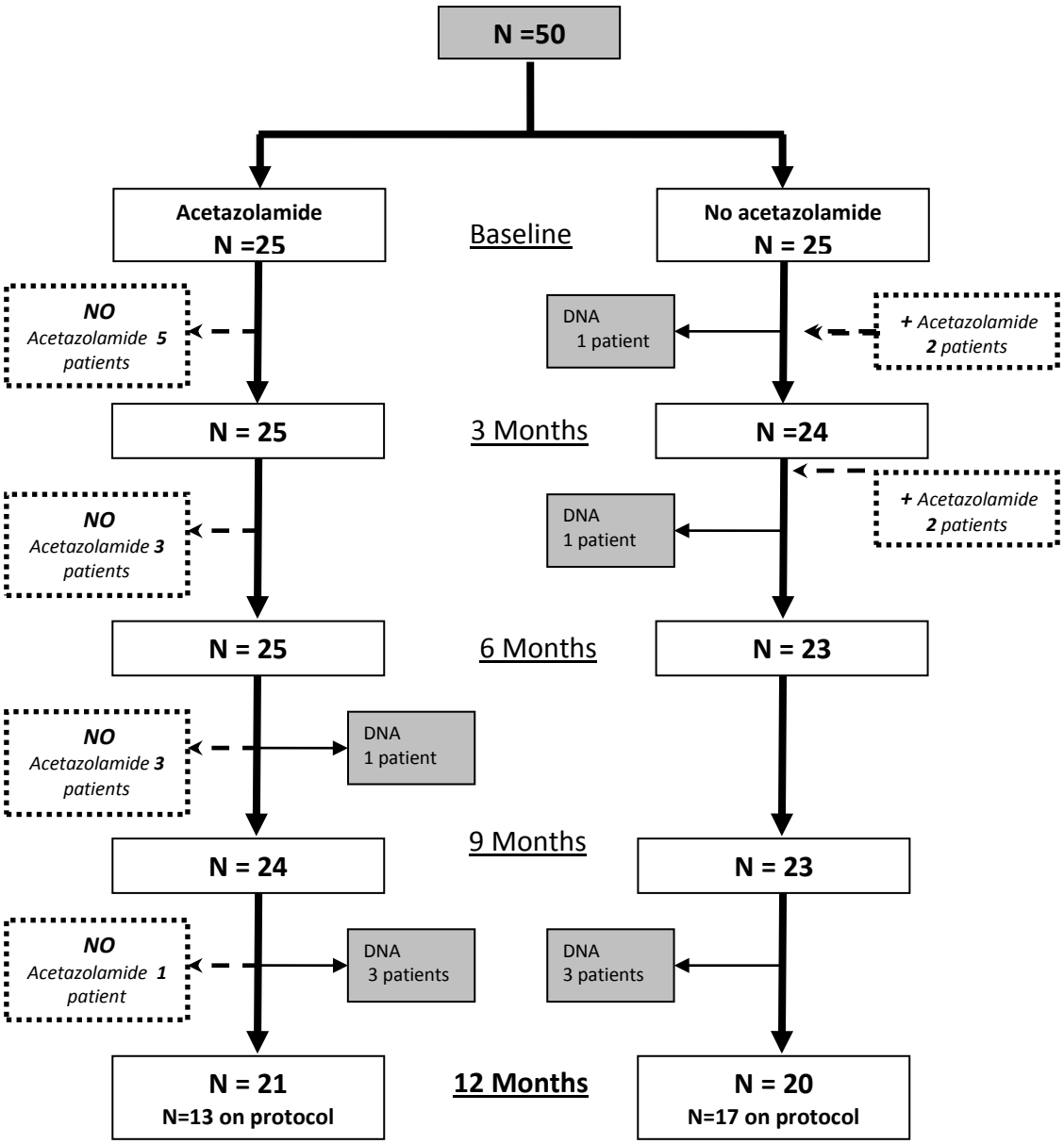


Figure 3.9 Disposition of patients in the IIH Trial. N = number of patients, DNA = did not attend visit and was lost to further follow up

Compliance with treatment allocation is also indicated in Figure 3.9. Four patients allocated to no acetazolamide were subsequently prescribed it during the trial as detailed in Table 3.9.

Table 3.9 Addition of acetazolamide during trial period

Timing	*Dose*	*Stated reasons*	*Notes*
Baseline + 2 weeks	750mg	Worse visual field Persistent headache Reduced visual acuity	Dose increased to 1000mg at 6-months. Further increase to 1500mg at 9-month visit
Baseline + 12 weeks	250mg	Persistent headache	Added outside trial. 3-month visit delayed by 5 weeks
3-month visit	500mg	Persistent disc swelling Blurred vision	Patient dropped out of trial after 9-month visit
3-month visit	500mg	Persistent headache	Dose increased to 750mg at 6-month visit due to worsening papilloedema, reduced to 500mg at 9-month visit

In two cases it was added prior to the 3-month visit and in two cases, at the 3-month visit. Reasons for adding acetazolamide included persistent headaches (3), disc appearance (1), reduced visual acuity (1), deteriorating visual field (1) and persistent blurred vision (1). One patient had acetazolamide added by their neurologist outside the trial.

Seven of the patients initially allocated to acetazolamide had their dose increased. All seven had starting doses of 500mg in 24 hours, increased to 1000mg in six cases and to 1500mg in one. The first dose increase occurred within the first three months in all cases. Overall in the study the dose of acetazolamide ranged from 250mg to 1500mg in 24 hours.

In the acetazolamide group, 12 patients discontinued or never started the drug. Reasons documented were patient preference (4), non-compliance from the outset (3), adverse

effects (2), planned pregnancy (2) and insertion of VP shunt (1). One patient reporting adverse effects (nausea) stopped acetazolamide before the 3-month visit, restarted it at the 6-month visit, but reduced the dose again at the 9-month visit due to further nausea. The other patient stopped the drug before the 3-month visit due to a the side effect of tingling fingers, restarted it at that visit at 250mg, discontinued it at 6-months due to pregnancy, which was terminated, then restarted it after the 9-month visit due to worsening headache.

3.3.6 Outcome

3.3.6.1 Final Outcome

Intention-to-treat analysis of the Final Outcome at 12-months showed: in the acetazolamide group, nine patients were in remission, three had active – improving IIH, eight had active – stable IIH and none had active – deteriorating IIH (table 3.10). In the control group, eight patients were in remission, two had active – improving IIH, six had active – stable IIH and three active – deteriorating IIH.

Table 3.10 Final Outcome by allocation: numbers of patients in each category are shown

	Final Outcome			
Allocation	**Remission**	**Improving**	**Stable**	**Deteriorating**
Acetazolamide	9	3	8	0
No Acetazolamide	8	2	6	3

A Mann-Whitney U test showed no significant difference between the treatment arms (p=0.5). Further analysis with treatment arm determined by acetazolamide use three months before the final visit, also showed no significant difference (p=0.8).

To obtain estimated confidence intervals for the treatment effect, categories were grouped into remission/improving and stable/deteriorating, and the odds ratio was 0.7 in favour of acetazolamide (95% CI 0.2, 2.6).

3.3.6.2 Final Status Score

Each patient was assigned a final score based on the sum of the other final status scores (headache, tinnitus, visual obscurations, visual acuity, visual field and optic disc), with 0 = best rating, 1 = intermediate rating and 2 = worst rating. A t-test was used to compare these sums between the two treatment arms. The mean Final Status Score (range: 0 best to 12 worst) was 2.6 in the acetazolamide arm compared with 2.9 in the control arm (p=0.6).

To assess the influence of the six final status scores with the upon the assigned overall IIH status, Final Outcome, frequency tables were drawn up (see tables 3.11a to 3.11f.) Somers' D statistic was calculated in each case, where 1 is total concordance between the variables and -1 is total discordance. The strongest concordance was for visual field score (D=0.66), followed by optic disc score (D=0.59), headache (D=0.39), tinnitus (D=0.33), visual obscurations (D=0.19), and visual acuity (D=0.05).

Table 3.11a Frequencies of visual field status categories by final outcome

		Final Outcome			
		IIH in remission	Active IIH improving	Active IIH stable	Active IIH deteriorating
Final Visual Field Status	Normal	15	3	4	0
	Abnormal, stable	2	2	9	3
	Abnormal, deteriorating	0	0	0	0

Table 3.11b Frequencies of optic disc status categories by final outcome

		Final Outcome			
		IIH in remission	Active IIH improving	Active IIH stable	Active IIH deteriorating
Final Optic Disc Status	Normal	10	3	2	0
	Abnormal, stable	7	2	12	1
	Abnormal, deteriorating	0	0	0	2

Table 3.11c Frequencies of headache status categories by final outcome

		Final Outcome			
		IIH in remission	Active IIH improving	Active IIH stable	Active IIH deteriorating
Final Headache Status	Absent	11	2	5	0
	Present, stable	5	3	5	1
	Present, deteriorating	1	0	4	2

Table 3.11d Frequencies of TVO status categories by final outcome

		Final Outcome			
		IIH in remission	Active IIH improving	Active IIH stable	Active IIH deteriorating
Final TVOs Status	Absent	16	4	11	3
	Present, stable	1	1	3	0
	Present, deteriorating	0	0	0	0

Table 3.11e Frequencies of tinnitus status categories by final outcome

		Final Outcome			
		IIH in remission	Active IIH improving	Active IIH stable	Active IIH deteriorating
Final Tinnitus Status	Absent	12	2	3	2
	Present, stable	4	3	9	0
	Present, deteriorating	1	0	2	1

Table 3.11f Frequencies of visual acuity status categories by final outcome

		Final Outcome			
		IIH in remission	Active IIH improving	Active IIH stable	Active IIH deteriorating
Final Visual Acuity Status	Normal	15	4	11	3
	Abnormal, stable	2	1	3	0
	Abnormal, deteriorating	0	0	0	0

The final headache status was also compared with the final pain score, shown in table 3.12.

Table 3.12 Final Pain Score compared to Final Headache Status

		Final Headache Status		
		Absent	Present, stable	Deteriorating
Final Pain Score	***1***	18	0	0
	2	0	2	1
	3	0	2	0
	4	0	2	0
	5	0	2	1
	6	0	1	1
	7	0	0	0
	8	0	1	1
	9	0	0	1
	10	0	0	1

3.3.6.3 Individual Outcomes

3.3.6.3.1 Clinical

Clinical features and measured outcomes were compared as measured at baseline and at the final visit, shown in table 3.13. There were no differences between the two allocation arms. Figure 3.10 shows the change in prevalence of headache, obscurations, diplopia, tinnitus, visual loss and papilloedema as recorded at each trial visit.

Table 3.13: Individual outcomes by allocation

	Acetazolamide		No Acetazolamide		
	Baseline (n=25)	*Final (n=21)*	*Baseline (n=25)*	*Final (n=20)*	*Difference between arms, (95% CI)§*
Headache %	68	43	72	65	0.42 (0.12, 1.4)
Headache VAS (mean)	3.5	2.3	4.9	3.7	1.0 (-1.8, 3.7)
TVOs %	68	10	60	10	0.95 (0.12, 7.3)
Tinnitus %	56	60	56	60	1.00 (0.29, 3.5)
Diplopia %	16	0	28	5	0.12 (0.002, 6.2)
Visual loss %	24	0	28	10	0.12 (0.007, 2.0)
Papilloedema %	100	67	100	65	1.07 (0.30, 3.8)
Left LogMAR	0 (-0.20–0.40)	0 (-0.10–0.2)	0.05 (-0.24 –0.38)	0 (-0.2–0.64)	0.03 (-0.09, 0.15)
Right LogMAR	0 (-0.20–0.32)	0 (-0.18–0.2)	0.01 (-0.22–0.36)	-0.08 (-0.2–0.36)	0.04 (-0.08, 0.16)
Left MD *	-1.47 (-7.8–0.94)	-0.71 (-3.98–0.67)	-2.91 (-10.46–0.14)	-2.24 (-5.91–0.78)	0.2 (-1.0, 1.4)
Right MD *	-1.53 (-6.02–0.75)	-0.29 (-4.50–0.98)	-2.57 (-9.9– -0.24)	-1.16 (-8.04–0.72)	0.0 (-1.1, 1.1)
Left CS (median only)	1.65	1.80	1.65	1.65	-0.3 (-0.6, 0.0)
Right CS	1.65	1.80	1.65	1.65	-0.2 (-0.5, 0.0)
Binocular CS	1.80	1.95	1.80	1.95	-0.3 (-0.7, 0.1)

Unless specified, medians and ranges are given. Baseline = baseline examination; Final = 12-month examination; VAS = headache pain visual analogue score (1=no pain, 10=worst); TVOs = transient visual obscurations; LogMAR = visual acuity as logarithm of minimum angle of resolution; MD = mean deviation on automated perimetry; CS = Contrast Sensitivity (Pelli Robson score);
*Excludes outlying data from one patient with baseline MD values of -21.15 left and -17.06 right who was subsequently lost to follow up.
§Differences between dichotomous variables (with % figures) are shown as Peto odds ratios based on final visit data, with a number <1 indicating benefit for acetazolamide. For continuous variables, differences shown are means, based on change from baseline, with numbers <0 indicating benefit for acetazolamide.

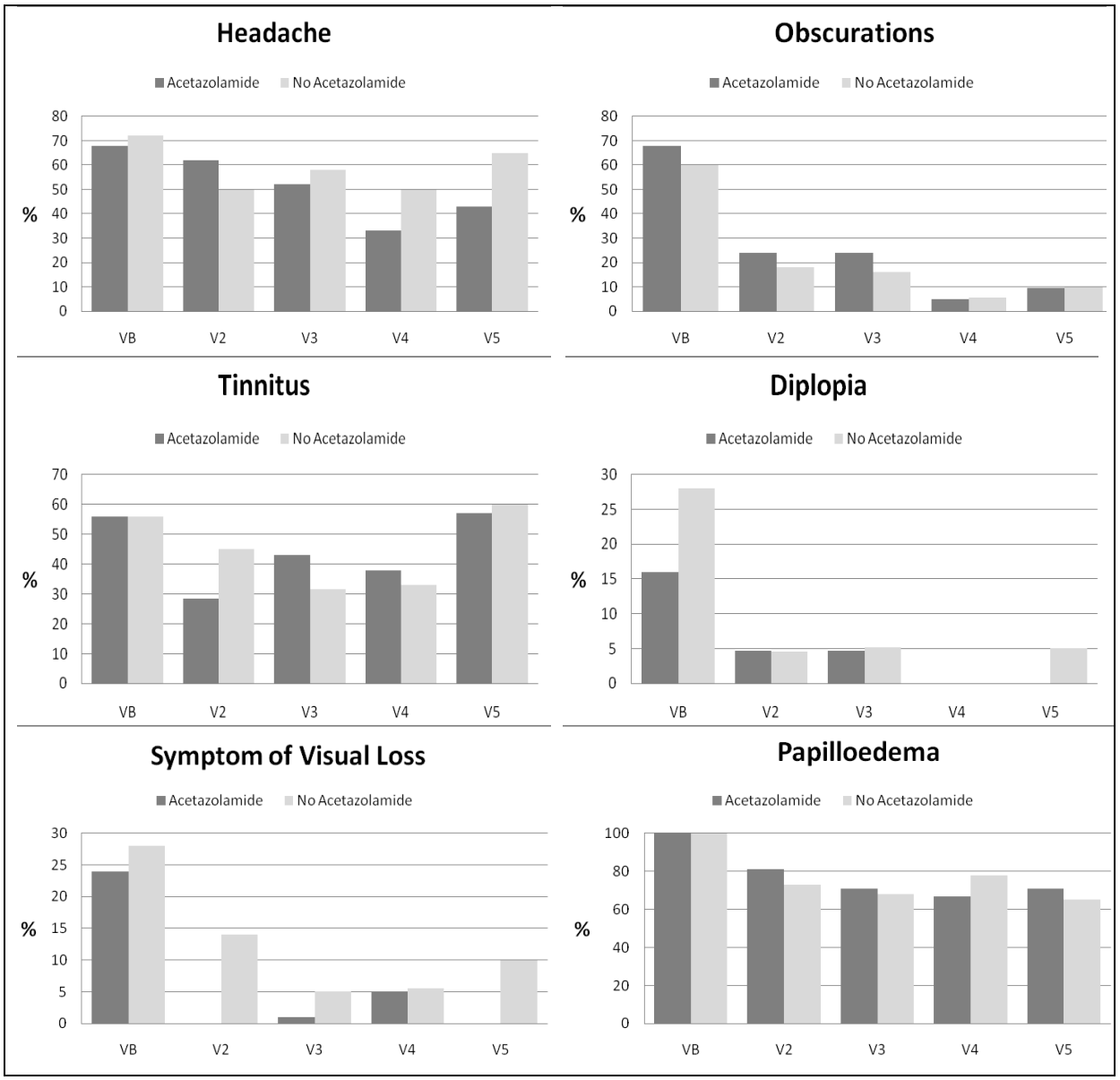


Figure 3.10 Change in clinical features by visit and allocation
VB=baseline visit, V2=3-month visit, V3=6-month visit, V4=9-month visit, V5=12-month, final visit.

More patients were recorded as having tinnitus at the final visit than at the start of the trial. As shown in table 3.14, a total of 12 patients from each allocation arm had tinnitus documented as present at the 12-month visit. Nine patients had no tinnitus at the start of the trial, but were recorded as having it by the final visit. There was a discrepancy between tinnitus recorded as present / absent on the symptom checklist and the final status scoring

sheets. When the final tinnitus status (absent, present-stable or deteriorating) was examined amongst the 24 patients who had the symptom tinnitus recorded as present at the 12-month visit, the status 'absent' was seen in four cases.

Table 3.14 Patients with tinnitus at the final (12 month) visit. A=acetazolamide, C=control, VB=baseline visit, V2=3-month visit, V3=6-month visit, V4=9-month visit, V5=final visit.

	Allocation	Presence / absence of tinnitus					Final Tinnitus Status	Final IIH Outcome
		VB	V2	V3	V4	V5		
1	A	+	+	+	+	+	Absent	IIH in remission
2	C	+	+	+	+	+	Absent	IIH in remission
3	C	-	+	+	+	+	Absent	IIH in remission
4	C	+	-		-	+	Absent	Active IIH deteriorating
5	A	-	-	-	+	+	Deteriorating	Active IIH stable
6	A	-	+	+	-	+	Deteriorating	Active IIH stable
7	A	-	-	+	+	+	Deteriorating	IIH in remission
8	C	+		-		+	Deteriorating	Active IIH deteriorating
9	A	+	+	+	+	+	Present, stable	IIH in remission
10	A	+	-	-	-	+	Present, stable	Active IIH improving
11	A	-	-	-	-	+	Present, stable	IIH in remission
12	A	+		?	+	+	Present, stable	Active IIH stable
13	A	+		-	-	+	Present, stable	Active IIH stable
14	A	+	+	+	+	+	Present, stable	Active IIH stable
15	A	-	-	-	-	+	Present, stable	Active IIH improving
16	A	-		+		+	Present, stable	Active IIH stable
17	C	+	+	+	+	+	Present, stable	IIH in remission
18	C	+	-	-	-	+	Present, stable	Active IIH stable
19	C	+	+	+		+	Present, stable	Active IIH improving
20	C	+	+	+	-	+	Present, stable	Active IIH stable
21	C	-	+	-	+	+	Present, stable	Active IIH stable
22	C	+	+	-	-	+	Present, stable	Active IIH stable
23	C	+	+	+	+	+	Present, stable	Active IIH stable
24	C	-	-		-	+	Present, stable	IIH in remission

Visual fields were compared at each visit for all patients (excluding one outlier value, as previously). Analysis of the mean MD values from the Humphrey automated visual fields showed significant improvement from baseline to final visit for both left MD (p=0.017) and right MD values (p=0.001). Mean MD values for each eye, by allocation, are shown in Figure

3.11. Whilst the values in the No Acetazolamide group appear greater the difference was not significant (p=0.22).

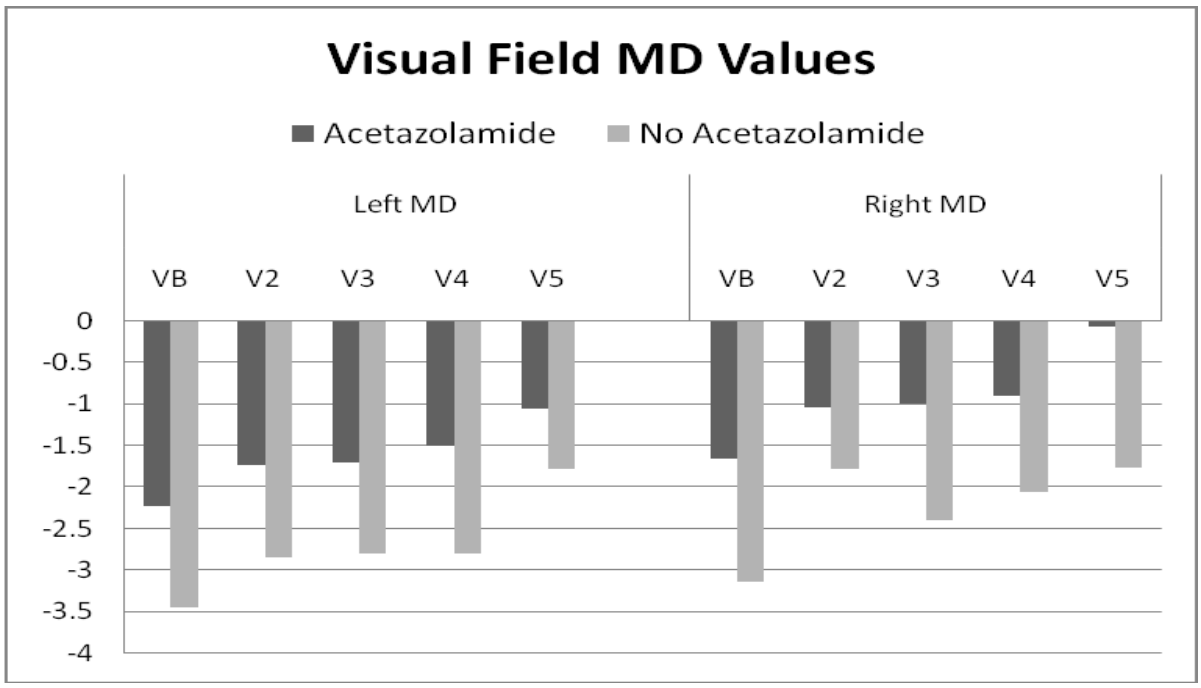


Figure 3.11 Mean MD values by visit and allocation.

3.3.6.3.2 Health-Related Quality of Life

SF-36 scores for all patients, regardless of allocation, were compared at baseline and at the final (12-month) visit, as shown in table 3.15. Only SF36 Pain and SF36 Change in Health showed significant improvement. The mean HADS anxiety and depression scores amongst all patients at baseline and at the final visit did not differ significantly (table 3.16). Similarly there was no difference between the EuroQoL self assessment and EQ5D mean scores at baseline and final visit (table 3.17.)

Table 3.15 Mean SF36 scores at baseline and final visit (all patients)

	Baseline visit n=48	*12-month visit n=38*	*P*
Physical Function	79.9	85.0	0.36
Role-Physical	69.5	76.0	0.16
Role-Emotional	77.2	78.5	0.90
Social Function	70.3	70.8	0.86
Mental Health	64.4	68.7	0.29
Energy Vitality	51.6	52.5	0.59
Pain	57.8	72.2	**0.02**
General Health Perception	57.6	59.8	0.64
Change in Health	47.8	59.7	**0.01**

Table 3.16 Mean HADS scores at baseline and final visit (all patients)

	Baseline visit n=48	*12-month visit n=38*	*p*
Anxiety Score	7.4	6.7	0.37
Depression Score	4.2	4.2	0.91

Table 3.17 Mean EuroQoL scores at baseline and final visit (all patients)

	Baseline visit n=46	*12-month visit n=36*	*p*
EuroQoL EQ5D visual analogue	67.0	70.8	0.5
EuroQoL EQ5D	0.7	0.8	0.3

The scores for each measure of health-related quality of life were examined by allocation and by visit as shown in Figures 3.12, 3.13, 3.14, 3.15 and 3.16. There were no significant differences between the allocation arms at any visit for any of the measures.

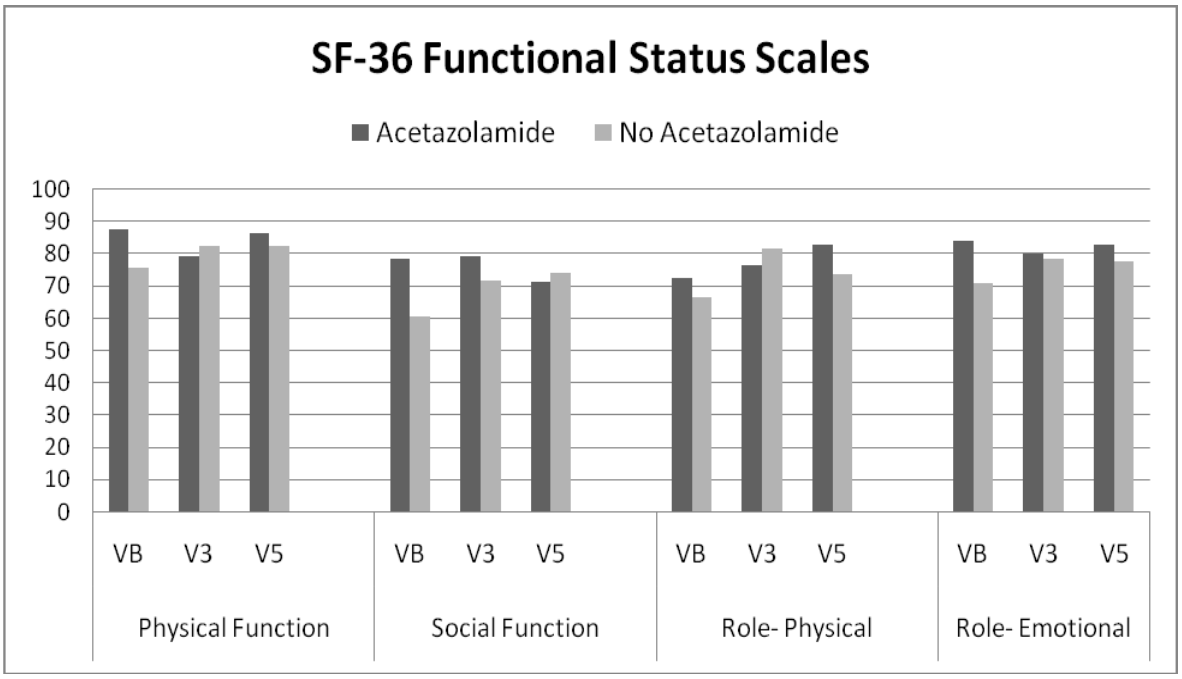


Figure 3.12 Mean scores amongst functional status SF-36 summary scales by visit and allocation. VB=baseline visit, V3=six-month visit, V5=final visit

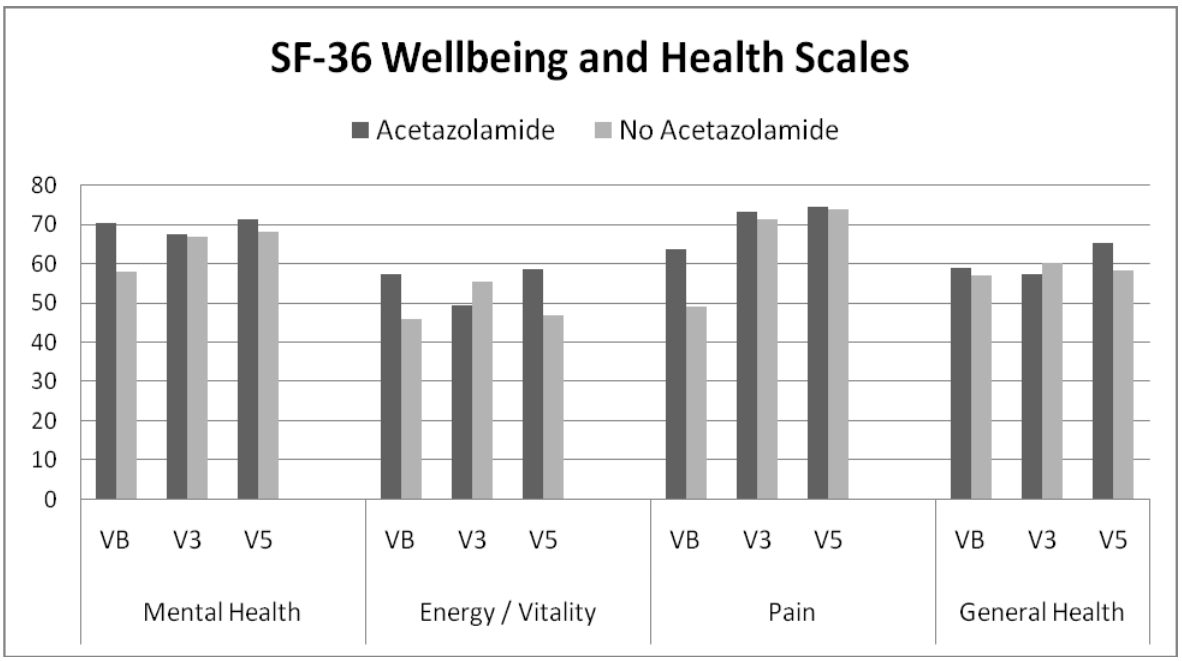


Figure 3.13 Mean scores amongst wellbeing and health SF-36 summary scales by visit and allocation

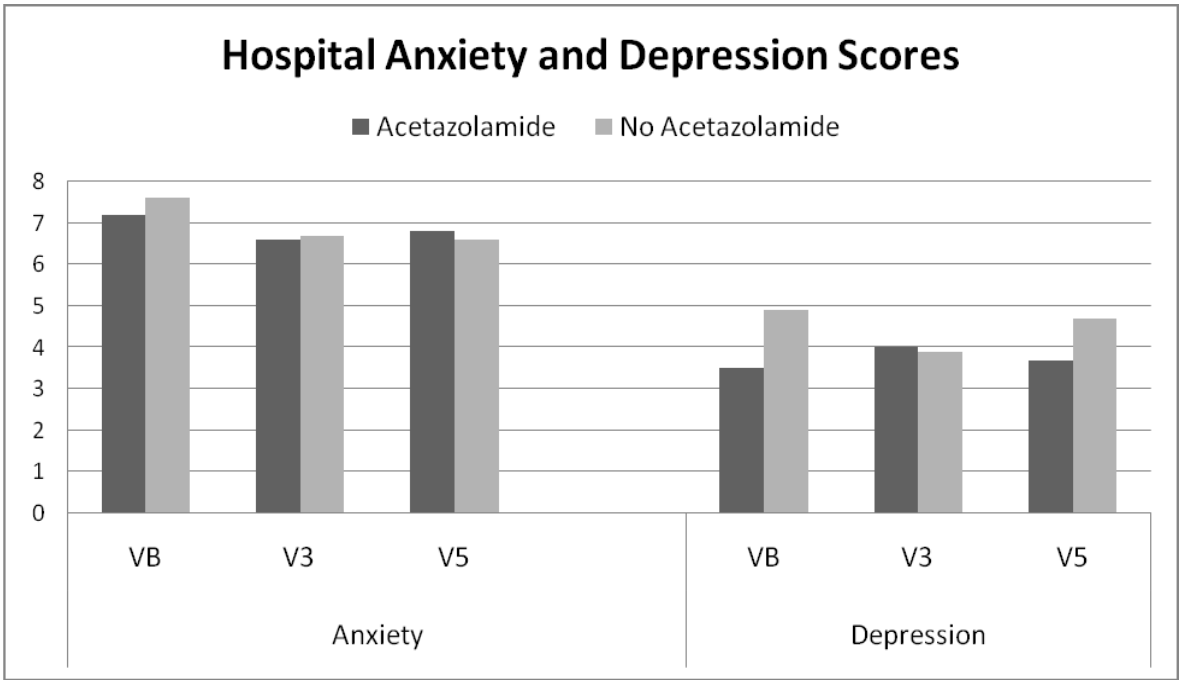


Figure 3.14 Mean HADS scores by visit and allocation. Scores are interpreted as 0-7 normal, 8-10 borderline and 11-21 abnormal for each

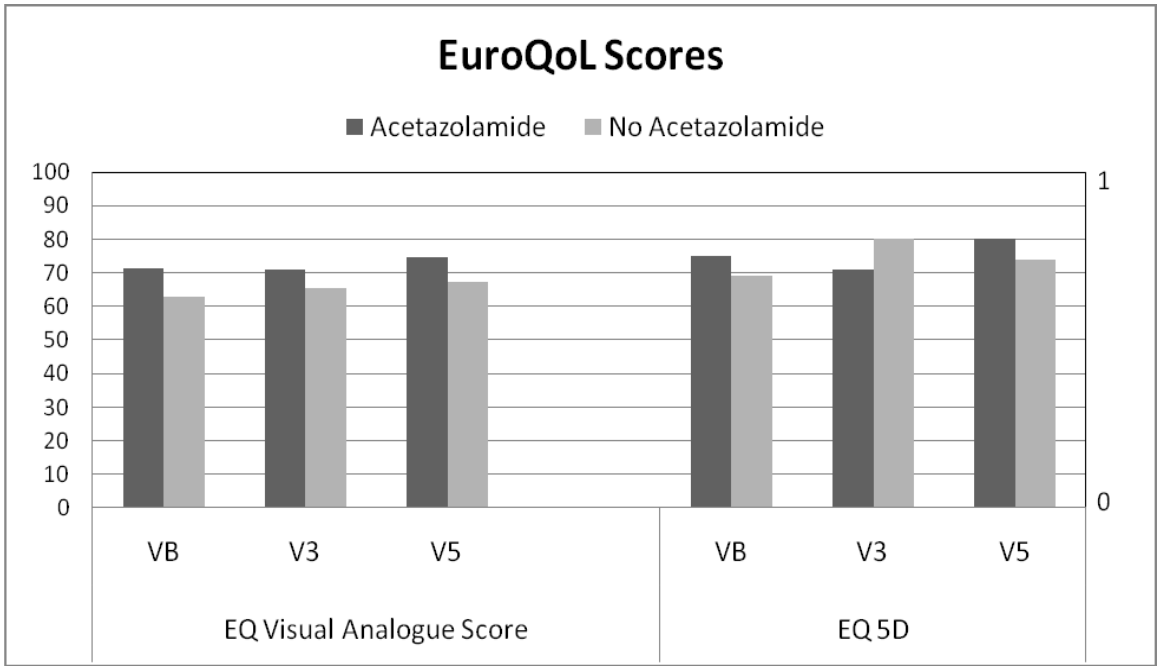


Figure 3.15 Mean EuroQoL scores by visit and allocation. EQ VAS ranges from 0 (worst) to 100 (best), EQ 5D from 0 to 1, where 1 represents a perfect state.

Table 3.18 shows the number of patients with HADS scores in each of the three categories at the three visits. The total numbers of patients completing questionnaires at each time point varied, so percentages are also given. The ratio of the total number of scores in the borderline and abnormal categories for anxiety, to the same total for depression, was 2.3.

Table 3.18 Number of patients in each category of HADS score, by allocation and visit. VB=baseline visit, V3= six-month visit, V5 = final visit, A = acetazolamide, C=control.

	VB		**V3**		**V5**	
	A	*C*	*A*	*C*	*A*	*C*
Anxiety: Normal (0-7)	15 (68%)	11 (58%)	13 (76%)	11 (61%)	13 (65%)	10 (62%)
Borderline (8-10)	2 (9%)	3 (16%)	0 (0%)	3 (17%)	2 (10%)	3 (19%)
Abnormal (11-21)	5 (23%)	5 (26%)	4 (24%)	4 (22%)	5 (25%)	3 (19%)
Depression: Normal (0-7)	21 (88%)	19 (83%)	17 (94%)	15 (83%)	17 (81%)	11 (79%)
Borderline (8-10)	1 (4%)	1 (4%)	0 (0%)	2 (11%)	3 (14%)	2 (14%)
Abnormal (11-21)	2 (8%)	3 (13%)	1 (6%)	1 (6%)	1 (5%)	1 (7%)

3.3.6.3.3 Repeated Measures Analysis

Repeated measures analysis was used to examine the effects of treatment allocation on each of the following variables, as measured at each visit during the trial: headache pain score, summed number of symptoms present scored out of seven (headache, tinnitus, visual obscurations, visual loss, diplopia, papilloedema and other), visual acuity (right, left), contrast sensitivity (right, left, binocular), visual field MD (right, left), HADS score, EQ-5D visual analogue score, EuroQol EQ-5D score and SF-36 domains (table 3.19.) Of these 21 comparisons, only one (contrast sensitivity, right) was significant at the $p<0.05$ level.

Table 3.19 Repeated measures analysis summary

Variable	Advantage for Acetazolamide	p-value
Headache Pain Score	-1.4	0.13
Summed Number of Symptoms	-0.04	0.94
Left LogMAR	-0.03	0.38
Right LogMAR	-0.01	0.80
Left Cont. Sens	0.14	0.14
Right Cont. Sens	0.13	0.03
Binoc. Cont. Sens	0.18	0.11
Left Mean Deviation	-0.16	0.71
Right Mean Deviation	-0.43	0.30
EuroQOL EQ5D visual analogue	-3.1	0.67
EuroQOL EQ5D	-0.1	0.13
SF36 Physical Function	-11.9	0.09
SF36 Role limitation / physical problems	4.0	0.65
SF36 Role limitation / emotional problems	1.9	0.78
SF36 Social Functioning	-4.1	0.63
SF36 Mental Health	-1.6	0.78
SF36 Energy / Vitality	1.5	0.84
SF36 Pain	-6.8	0.47
SF36 General Health Perception	-1.4	0.81
HADS Anxiety score	-0.04	0.97
HADS Depression score	-0.35	0.69

Note: treatment effect signs have been adjusted so a positive score indicates advantage for acetazolamide

3.3.6.4 Surgical Intervention

Two patients required surgical intervention within a month of randomisation, one in each arm of the trial. Characteristics of the two patients are shown in table 3.20. A further patient had their final visit IIH status recorded as 'active, deteriorating' and was being considered for shunt insertion at the end of the trial.

Table 3.20 Characteristics of patients receiving surgical intervention during the study

	Patient 1	*Patient 2*
Gender	F	F
Age	23	28
BMI kg m^{-2}	44.9	32.6
CSF OP cm	60	30
Associated features	Prescribed erythromycin within 6 months of entry to study	Taking steroid inhalers for asthma
Baseline symptoms	Headache, Visual obscurations, tinnitus, visual loss	Headache, Visual obscurations
Headache VAS	8	2
Allocation	No acetazolamide	Acetazolamide
Baseline LogMAR acuity (left, right)	0.30, 0.34	0.22, 0.32
Baseline MD (left, right)	-21.15, -17.06	-1.72, -6.02
Documented reasons for surgery	Reduced vision	Worsening papilloedema Worsening symptoms New RAPD right eye
Timing of surgery (days post randomisation)	2	34
Additional information	Lost to all follow-up after 3-month visit	Discontinued acetazolamide after shunt inserted

3.3.6.5 Pregnancies

There were 5 pregnancies during the trial, summarised in table 3.21. Three patients in the acetazolamide group were recorded as pregnant at the nine-month visit. Two had stopped the medication, and two had elective termination of pregnancy, one whilst continuing to

take acetazolamide. In the control group, one patient was recorded as pregnant by the three month visit, delivering a healthy baby during the trial and another was noted to be pregnant at the six-month visit then in healthy pregnancy at the final assessment.

Table 3.21 Pregnant patients during the trial. A=acetazolamide, C=no acetazolamide, T.O.P= termination of pregnancy, V3=6-month trial visit, V4=9-month trial visit

	Allocation	*Pregnancy status (at final visit)*	*Final Status (Symptom Score)*	*Final Outcome*
1	A	T.O.P after V3	2	Active, improving
2	A	T.O.P after V4	1	Active, improving
3	A	2nd trimester	1	Remission
4	C	Delivered after V4	0	Remission
5	C	2nd trimester	4	Active, stable

3.3.6.6 Weight change

Table 3.22 Availability of weight data by visit and by total number of recorded values in trial; n=number of patients

Visit	**n**	***%***		**Total no. of weights recorded**	**N**	***%***
Baseline	50	*100*		1	1	*2*
3 month	40	*80*		2	4	*8*
6 month	35	*70*		3	9	*18*
9 month	36	*72*		4	17	*34*
12 month	38	*76*		5	19	*38*

The availability of data on body weight is shown in table 3.22. There was an overall weight reduction in both allocation groups. In the acetazolamide group, mean weight fell from 106.9kg at baseline to 100.7kg at the final visit (a mean loss of 6.2kg, 5.8%.) In the control arm, mean weight at baseline was 94.8kg and at 12-months, 91.5kg (mean weight loss of 3.3kg, 3.5%.) The mean BMI and as well as the mean change in weight were examined by repeated measures analysis (figures 3.16 and 3.17) and there was no difference between the allocation arms.

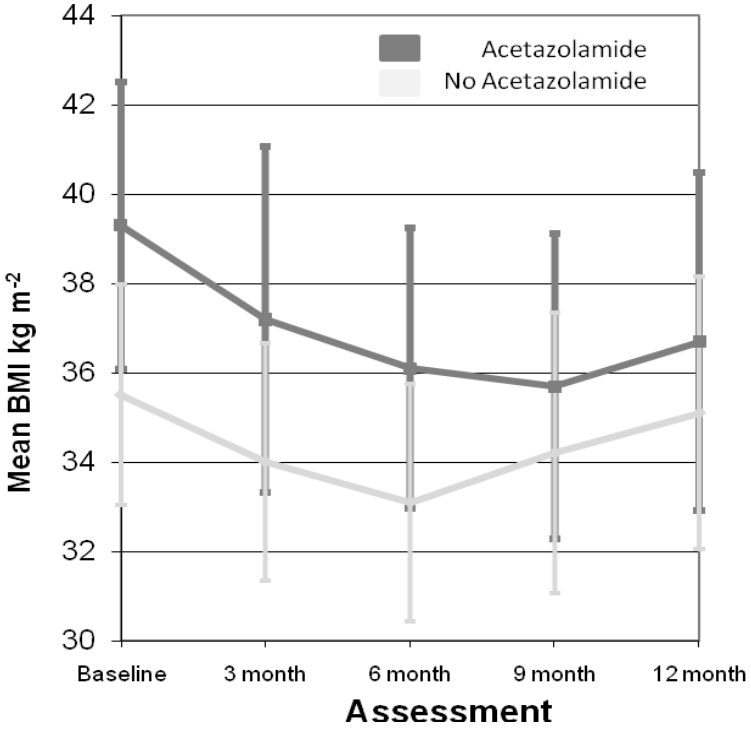


Figure 3.16 Average Body Mass Index by allocation throughout the trial. Error bars show 95% confidence intervals

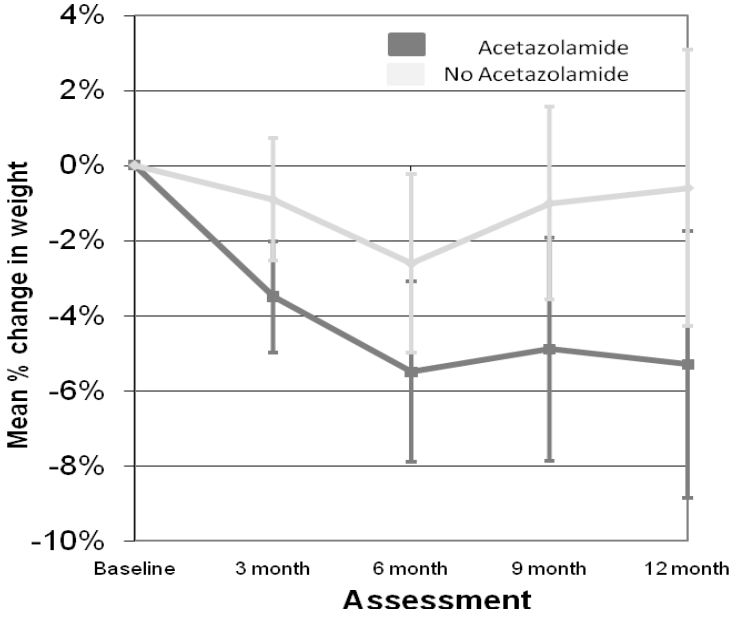


Figure 3.17 Average change in weight by assessment and allocation. Error bars show 95% confidence intervals

Change in weight ranged from 12.5kg gain to 23.5kg loss, median 1.1kg. More patients lost (n= 30) than gained weight (n=19), as shown in figure 3.18.

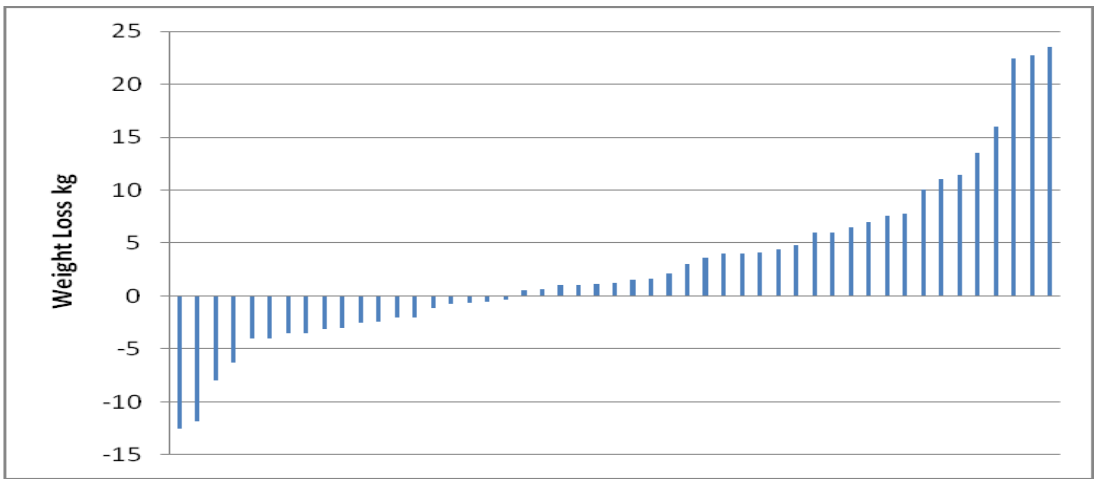


Figure 3.18 Overall change in weight during trial. Lines represent the difference between the last weight recorded and the baseline weight in kg for individual patients (n=49)

In total, 38 patients had final outcome and weight at 12-month visit recorded. Amongst 12 patients who had lost 5% weight or more by the end of the trial, eight (67%) had a final outcome of 'in remission' or 'improving'. This compares with 6 out of 12 patients (50%) who had lost between 0 and 5% weight and 7 out of 14 patients (50%) who had gained weight. Cuzick's test for trend was applied to the ungrouped data and revealed no significant trend (p=0.3).

3.3.7 Sample Size Calculation

One purpose of this pilot study was to inform the planning of a definitive trial. Based on the data for the final IIH status, preliminary calculations were undertaken in an attempt to predict how many patients would be required to show a treatment effect, should one exist. The dropout rate and protocol non-compliance were taken into account in the calculations,

performed by grouping the four outcome categories into two and performing a chi squared test. Final IIH outcome was regarded in two categories: (1) 'in remission' and 'active, improving' or (2) 'active, stable' and 'deteriorating'. In order to detect an improvement of 20% in the treatment arm, such that 20% more patients were in category (1), around 300 patients in total would be required, based on 90% power and significance set at p=0.05.

As an alternative to grouping the best two and worst two outcome categories, a Mann-Whitney *U* test can be applied to the four-way outcome data to improve sensitivity. This shows that 240-270 patients would be required to detect a 20% difference. Approximately 120 patients would be needed to detect a difference of 30%. The calculations are based upon an intent-to-treat population, such that observed improvement allows for dilution of any treatment effect by non-compliance.

3.4 Discussion

This study prospectively recruited 50 patients to the first randomised controlled trial in IIH. Whilst the small numbers in the study preclude any firm conclusions about the benefits or detriment of treatment, the data is informative on several issues pertinent to the study of patients with IIH.

3.4.1 Recruitment

Rates of recruitment to the study were slower than anticipated. Recruitment of 50 patients was projected over a 12 month period, but in reality, reaching this number of patients took 23 months. A mean rate of two patients recruited per month seems surprising, given the numbers of centres enrolled in the study and resulting catchment population. No published

figures exist for direct comparison, although it is interesting to note that the numbers involved in the major published prospective studies were not dissimilar. In the Libyan case-control study by Radhakrishnan et al, (1993) 40 patients were seen between 1987 and 1989; In that of Wall and George (1991), it took from 1982 to 1988 to recruit 50 patients with IIH who met the entry criteria. The study period in the trial of acetazolamide and topiramate in 40 patients was just over 4 years. (Celebisoy et al., 2007) Whilst these studies had somewhat lower rates of recruitment than that of the current study, they were all conducted from single treatment centres, so the figures are probably comparable.

Detailed information regarding patients who failed to meet the criteria for inclusion following initial screening was only available for the patients seen at the Birmingham centres. Over a quarter of patients (9 in 34) could not be randomised because they were already receiving acetazolamide. Wide publicity preceded and continued throughout the study, in the form of posters and leaflets displayed in clinical areas as well as presentations about the trial in professional meetings. The advice to withhold the use of acetazolamide prior to discussing patients with the neurology or neuro-ophthalmology teams, all of whom were well informed about the trial, was widely disseminated amongst the relevant acute hospital teams. Despite this, several patients were prescribed acetazolamide at a very early stage of admission and were subsequently ineligible for entry to the study. This highlights the common use of acetazolamide despite no evidence base for its use in IIH.

Three patients appeared on initial assessment to be eligible for the study but were then found to have no papilloedema when assessed in the neuro-ophthalmology clinic. It is necessary to appreciate the patient pathway of entry to the trial in Birmingham to interpret this finding. Most patients were admitted acutely for their diagnostic investigations,

including scans and lumbar puncture. Some, but not all, received their detailed neuro-ophthalmology assessment immediately following the lumbar puncture. A number of patients were discharged from hospital to be seen shortly afterwards in the neuro-ophthalmology outpatients clinic, resulting in a delay between the lumbar puncture and the assessment of papilloedema using a slit lamp. It is possible that the diagnostic lumbar puncture resulted in a reduction in the intracranial pressure sufficient to reverse the optic nerve swelling, such that papilloedema was no longer present at follow up. Uncertainty surrounds the mechanism and timing of both papilloedema formation and its resolution upon lowering of the pressure, due to a lack of research evidence. However clinical experience and anecdotal reporting suggests that a subset of patients with IIH do experience resolution of their symptoms and clinical signs, including papilloedema, following a single lumbar puncture. Whether a slow leakage of CSF via needle punctures in the dura also contributes is unclear. An alternative explanation for the absence of papilloedema at slit lamp examination could simply be that the papilloedema was initially misdiagnosed, if ophthalmoscopy during the acute admission led to a falsely positive finding.

Although IIH without papilloedema (IIHWOP) is now a recognised clinical entity, (Bono and Quattrone, 2009) no patients with absent papilloedema were recruited to this trial. The absence of papilloedema in the three screened patients reported was accompanied by other features casting doubt on the diagnosis, such that it was appropriate to exclude them from the study.

3.4.2 Patient Characteristics

3.4.2.1 Demographics

Age and gender characteristics of the patients in the trial were as expected. The female to male ratio was 12.5:1, exactly that of the study by Wall and George (1991) and similar that of the largest review to date, by Bruce et al (2009) of 10.1:1.

All patients were overweight, with the exception of two (BMI 23.7 and 24.5 kgm^{-2}). 46 of the patients (92%) had body mass index at baseline in the obese range (greater than 30 kgm^{-2})

Opening CSF pressure ranged from 25 to 78 cm. Five patients had a pressure of 40 cm recorded and a further six had pressure of "greater than 40 cm" recorded. This is likely to reflect the method of CSF pressure measurement, using 20 cm manometers. To record values above 40 cm requires the use of three manometer tubes attached together. It is likely that for some of the six patients at least, measurement was stopped when the top of the second manometer was reached, instead of additional tubing recording values of greater than 40cm more accurately. True maximum pressures in this cohort could therefore have been higher.

3.4.2.2 Associated medical conditions

The prevalence of systemic hypertension was comparable to that of other published studies. Eight of the 50 patients reported hypertension, in the Wall and George study (1991) it was recorded in 13 of 50 patients and by 11 of 76 patients (14.5%) in that of Radhakrishnan et al. (1993) All the hypertensive patients in this study with the exception of one were older than the mean study age of 31 years, with a mean of 49.5 years. The figures are unremarkable given that hypertension is common, especially in association with obesity.

Hormonal dysfunction amongst the female patients was only evident in three cases (6.5%). Symptoms of polycystic ovary syndrome have been reported in over a third of female patients in some studies (Glueck et al., 2003) and irregular menses were reported by 30% of patients at presentation in the study by Radhakrishnan et al. (1993) A higher proportion of the patients reported current or recent use of hormonal medication. Over a quarter of women in the study were taking oestrogens as contraception or HRT (12 of 46 patients, 26%) and a further four (9%) had discontinued oral contraceptives within the preceding six months. A high prevalence of hormonal medication use seems likely amongst females of the age group reported and the study design does not permit further conclusions to be drawn about the significance of these values.

The seemingly low prevalence of reported menstrual disturbance in this study is most likely due to under-reporting. The baseline data collection did not include specific questions addressing menstrual function and any positive findings relied upon patients or assessing clinicians to volunteer the information as part of the medical history they felt to be relevant.

A similar explanation could account for the recording of only two instances of psychiatric symptoms amongst the 50 patients (depression in one, depression with panic disorder in another) and an isolated case of suspected obstructive sleep apnoea syndrome. The latter was reported in 4% of 655 women and 24% of 66 men in the study by Bruce et al,(Bruce et al., 2009) but the diagnosis was not specifically sought in this cohort.

3.4.2.3 Baseline Symptoms

Headache was present at baseline in a smaller proportion of patients than in many other large studies. 15 of the 50 patients had no headache on entry to the trial. Eight patients

noticed improvement or resolution of their headaches after the diagnostic lumbar puncture, thus the true prevalence of headache at presentation was somewhat higher. No specific features characterised the headaches reported, although four patients had headaches affected by posture, thought to be in keeping with raised intracranial pressure. The method of data collection was insufficient to provide detailed information about headaches in IIH; for this, specific headache questionnaires would have been required.

The same applies for the other symptoms (transient visual obscurations, tinnitus, diplopia and visual loss) upon which comment was invited during the study. Collection of descriptive data was dependent upon the assessing clinician volunteering detailed information and was not sought in a meticulous fashion in this study. Robust data collection on the individual symptoms characteristics would require specially designed methodologies.

There was only one completely asymptomatic patient, a 25 years black Caribbean female with BMI 31.1 kg m^{-2} and CSF opening pressure 39cm. Papilloedema was present on examination and it was commented that headache had been present initially but had resolved after the lumbar puncture. There were eight further patients who had lone presenting symptoms: visual loss (1), tinnitus (1), headache (2) or visual obscurations (4).

3.4.2.4 Baseline Visual Acuity

Median LogMAR acuity in both eyes for both allocation arms was 0 (normal). The total numbers of patients with LogMAR acuity of 0.2 or worse (equivalent to Snellen 6/9.5) were, for the left eye, 11 and the right eye, 10 out of the total of 50. Thus approximately 20% of the patients had some reduction of visual acuity, although in at least one patient, this was

due to conditions other than IIH. No patient had a LogMAR of more than 0.4 in either eye at baseline.

Corrected Snellen visual acuity was worse than 6/9 in at least one eye in eight (21%) of 42 patients at initial and nine (24%) at the last follow up in one case note review. (Craig et al., 2001) In the largest published review of patients with IIH, the median LogMAR acuity in women was 0 (normal), but significantly worse in men, with median of 0.2. (Bruce et al., 2009) Amongst prospective studies, the best corrected Snellen acuity at the initial visit was abnormal in 4 (10%) of 40 patients, (Celebisoy et al., 2007) showed a moderate or severe decrease in 36 (24%) of 152 eyes in 76 female patients (Radhakrishnan et al., 1993) and worse than 20/20 in 12% of right eyes and 14% of left eyes in 50 patients. (Wall and George, 1991) (Wall, 1991).

Amongst the four male patients, left LogMAR values were 0, 0.04, 0.22 and 0.3, with corresponding right LogMAR values of 0, 0.04, 0.14 and 0.2. Thus half of the men in the study had acuities worse than the median value, although the numbers are too small to attach significance to the finding.

3.4.2.5 Baseline Contrast Sensitivity

Contrast sensitivity results were only available for 19 of the 50 patients studied, because the Pelli-Robson charts were only in use at the Birmingham trial centre. The majority of values were above 1.50 in keeping with normal results. Only two outlying values were seen. One patient had a right contrast sensitivity of 1.20, with normal left and binocular values at baseline. However this improved by the three month value to 1.80 and may have been effort

related. A second patient had a consistently low right sided contrast sensitivity of 1.05 in a severely amblyopic eye.

Contrast sensitivity measured using sinusoidal grating stimuli was shown to be abnormal in 16 of 37 non-amblyopic eyes from 20 patients with IIH, 12 of whom had normal visual acuity. (Bulens et al., 1988) In the same year, Verplanck et al (1988) found abnormal contrast sensitivities amongst 10 of 15 patients with acute IIH, in 18 eyes in total. Nine of these eyes had normal visual fields as well as visual evoked potentials. The absence of published data on contrast sensitivity measured by Pelli-Robson charts in IIH precludes further comment on the values seen in this study.

3.4.2.6 Baseline Visual Fields

Humphrey automated perimetry was performed on all patients in this study. One patient had markedly abnormal visual fields at the initial visit, with mean deviation (MD) values of -21.15 left and -17.06, right. This patient was treated with a VP shunt just two days after randomisation to no acetazolamide and unfortunately failed to attend for further trial visits or perimetry. These MD values were unusual for this study, the next highest value amongst other patients being -10.46.

The range of incidences of abnormal visual fields reported in the literature is broad. Earlier studies have documented lower incidences of visual field abnormality than more recent publications, but this may reflect the assessment strategies applied. Detailed examination of visual fields is likely to result in detection of a greater proportion of defects.

In the review of patients in Northern Ireland, an abnormality other than enlargement of the blind spot was recorded in 18 (62%) of 29 patients. (Craig et al., 2001) Rowe and Sarkies

(1998) noted visual field defects in 72% of 70 eyes by Goldmann perimetry and 89% of eyes using Humphrey automated perimetry in their prospective study.

Some authors have reported MD values from automated perimetry. On initial diagnosis, 76 patients in the study by Galvin and Van Stavern (2004) had mean MD values of -5.96 (right) and -6.58 (left), which the authors interpreted as 'moderate' defects. In the large series by Bruce et al, (2009) median values were 5 in women and 7.7 in men at baseline and 3.7 in women and 4.7 in men at the final visit.

The values recorded in this study were somewhat lower (less abnormal). Median left MD values at baseline were -1.47 (acetazolamide group) and -3.10 (control group), corresponding right MD values were -1.34 and -2.58. Overall, 37 (74%) of 50 patients had some finding on their baseline visual field that was determined by the perimeter software to be outside normal limits, (i.e. assigned a p value). Thus the prevalence of defects of any kind was similar to that of other studies, although the severity of the defects was probably less. This reflects the tendency of the trial to recruit patients with less severe IIH; patients with significant visual field defects were more likely to have been observed and managed outside the trial.

3.4.3 Outcome

3.4.3.1 Data completion

The overall dropout rate for the trial, based on the numbers of patients with complete data sets or completed final visit data, was approximately 20%. For each outcome measure in the study, a response rate of 80% or more was typical for recorded outcomes amongst the 50

patients over the five trial visits. Specific examples include Visual fields, completed in 210 out of a possible 250 cases (84%), LogMAR acuities measured in 206/ 250 (82%) and data on headache in 213 / 250 (85%). Contrast sensitivity was only available to 20 patients and data was present for 80 out of a possible 100 visits (80%). Completed questionnaires numbered 48 at baseline, 39 at the six-month visit and 29 at the final visit, giving 126 out of a possible 150 (84%).

There were some discrepancies between documentation of individual clinical features and the subjective assessments at the final visit. For example, in four patients, papilloedema was documented as present on the examination section of the final visit assessment forms, but the final optic disc status was recorded as 'normal'. Similar discrepancies were seen in the documentation of tinnitus (four patients) and obscurations (one patient), but not headache.

Numbers of patients attending each visit were similar regardless of allocated treatment. Inconsistencies in the documentation were also seen in both allocation arms with equal frequency. Thus data omissions and discrepancies are unlikely to have affected the overall results.

3.4.3.2 Acetazolamide compliance

The poor compliance with acetazolamide is of interest. Almost half (12 out of 25) of the patients assigned to receive acetazolamide discontinued the medication during the 12-month study period. Treating clinicians were responsible for determining the starting dose of acetazolamide and any subsequent dose titration. No patient received doses in excess of 1500mg/24 hours and all of the patients who discontinued the drug were receiving lower

doses than this. The high attrition rate is surprising given the widespread use of this drug in treating IIH and the relatively low doses employed in this study.

The published open-label study by Celebisoy et al (2007) compared acetazolamide and topiramate in 40 patients. No patients in this study were reported to have discontinued their medication due to adverse events. The most frequently reported side effects were fatigue and tingling of hands and feet. Daily doses of acetazolamide ranged from 1000 to 1500mg and a titration schedule starting with 500mg per day was used.

In the prospective study by Sorensen et al, (1988) 'nearly all' of 17 patients treated with daily doses of 750 to 1500mg acetazolamide had metabolic acidosis and experienced nausea and moderate paraesthesia of hands and feet. These side effects were reported as transient in most, but some patients required dose reduction and one patient had depression which warranted discontinuation of treatment. However, all patients received diuretic in addition to the acetazolamide, either furosemide 80mg or chlorthalidone 100mg daily. They were also all treated with potassium supplementation to overcome the hypokalaemia caused by diuretic. In this trial, none of the patients were receiving diuretics as well as acetazolamide; only one of the 50 patients was taking a diuretic (bendroflumethiazide) and they were randomised to the control arm.

It is possible that the severity of IIH amongst the patients in this study had an effect upon their tolerance of acetazolamide. Patients may be less likely to comply with prescribed treatment if they have few or no symptoms. Further examination of the patients who never took the medication or discontinued it through choice or due to side effects shows that two patients were totally asymptomatic, but the remaining seven had one, two or three symptoms, with headache as the most common. The final outcome was recorded for seven

of the patients; two were in remission, two had active, improving IIH, four had active stable IIH and none had deteriorating disease. Small numbers preclude further analysis of this subgroup of patients, but the levels of non-compliance seen probably reflect the lack of significant morbidity. It is also conceivable that other studies have under-reported compliance rates.

Amongst the patients initially allocated to receive no acetazolamide, four (16%) deviated from the protocol through the addition of acetazolamide. In all cases this was early on in the study, before or at the 3-month visit and all four patients continued the drug throughout the remainder of the trial period, at increased doses in two cases. Reasons for commencement of acetazolamide varied, although symptoms were a contributing factor in all cases, which may have impacted upon the patients' likelihood of continuing the medication.

3.4.3.3 Outcome by allocation

Our results showed no significant difference between treatment arms in terms of final outcome. Whilst the odds ratio for remission / improving was slightly in favour of acetazolamide (0.7, 95% CI 0.2, 2.9), the confidence interval was wide and our results would be consistent with either a treatment benefit or detriment. A wide confidence interval was not unexpected, given the number of patients in this pilot study. Comparison of the composite final status scores, which summarised symptoms and signs at the 12-month assessment, also showed no difference between treatment allocations. Furthermore, examination of outcome variables by a total of 21 repeated measures analyses failed to demonstrate a treatment effect. Although right contrast sensitivity showed a p value of 0.03,

this one significant result is entirely consistent with what would be expected by chance alone when carrying out 21 separate analyses.

In view of the relatively high level of non-compliance in the trial, additional analysis was carried out to examine in more detail the high dilution of the intervention effect. Patients were categorised into a treatment arm based on whether or not they were receiving acetazolamide in the three months prior to the final assessment. The results did not differ from the intention-to-treat analysis. A true per-protocol analysis, in which data was only analysed from patients receiving their allocated treatment throughout the trial, would have involved too few cases to be informative. Whilst all three patients described as deteriorating IIH at 12 months were in the deferred acetazolamide group and remained on protocol throughout the trial, (i.e. did not have acetazolamide added), the difference between the two treatment arms was not significant (p=0.5).

The trial was conducted as an open label study and control subjects did not receive placebo. Subjects and treating clinicians were also not blinded to the treatment allocation. This was in keeping with the original aim of the study, which was to pilot a pragmatic trial which would complement normal clinical practice. The possibility exists that this may have allowed performance and detection bias to influence the results. However, the trial design was kept as simple as possible to maximise recruitment, reduce expense and mimic 'real life' as far as possible. Such pragmatic designs are now in common usage in other neurological fields such as stroke (e.g. International Stroke Trials) and Parkinson's disease (eg PD MED and PD SURG.)

3.4.3.4 Surgical Intervention

Two of the 50 enrolled patients had surgical intervention during the course of the study, one in each randomisation arm. The surgery was carried out soon after recruitment in both (two days in one case and four weeks in the other). Both patients were female and obese and were referred for VP shunts due to concern over their visual function. One of the patients had MD values on initial perimetry that were considerably worse than any other values recorded in the whole study (left -21.15, right -17.06). Unfortunately the patient dropped out of the trial and did not undergo repeat perimetry. Both patients had LogMAR values towards the higher end of the range seen in the trial, indicative of some reduction in visual acuity. The patient for whom follow-up data was available showed improvement in acuity following surgery, from 0.22 to 0.10 in the left eye and 0.32 to 0.08 in the right. There was a corresponding improvement in their MD values from -1.72 and -6.02 before surgery to 0.37 and 0.06 at the final visit.

Three of the 34 patients screened for eligibility for the trial in the Birmingham centre were referred for immediate surgery and all received shunts during their initial hospital admission. The decision to proceed with surgery in these three cases was made by consensus amongst the admitting medical team, the senior neuro-ophthalmology consultants and the neurosurgeons regarding the risk of visual deterioration. It is not possible to extrapolate this data to estimate the proportion of patients with newly diagnosed IIH who have significant existing or threatened visual loss. Such information would be of great use, since it is precisely this group of patients for whom evidence based treatment is urgently needed. However, data on screened, ineligible patients was not collected prospectively in a sufficiently rigorous manner. There were undoubtedly patients with newly diagnosed IIH,

with varying degrees of visual loss or threat to their vision, who failed to reach the attention of members of the trial team during the recruitment period.

It is thus recognised that the trial design meant patients towards the benign end of the IIH clinical spectrum were recruited. Patients who had more severe visual abnormalities at screening, felt to require urgent intervention such as surgery, failed by definition to meet the inclusion criteria of uncertainty of the treating clinician. This trial therefore focussed on individuals with milder forms of IIH, amongst whom severe visual loss is uncommon.

3.4.3.5 Weight reduction

Weight was recorded at baseline in all patients. Due to the pragmatic design of the study and busy clinical setting, weight was not always documented subsequently (79.6% overall recording rate when averaged over the five visits) and may not always have been accurate, due to variations in clothing and weighing scales used. In addition, missed visits resulted in some loss of data, but 90% of patients had at least three separate values recorded. An overall weight reduction was more common: 19 patients gained weight and 30 patients lost weight. In most patients, the overall change was slight, with more than a 10% change in just seven patients.

All patients in this study were advised to follow a programme of weight reduction if they were overweight. It was considered unethical to include an arm in the trial in which overweight patients were not advised to lose weight. Whilst patients in the acetazolamide arm lost a little more weight, the difference was not significant. The patients had a slightly

higher mean BMI at the start of the trial (39.3, versus 35.5 in the deferred treatment arm) which may have impacted on the amount of weight lost.

A small number of published studies have demonstrated an association between weight reduction and clinical improvement in IIH. In the case review by Johnson et al (1998) six obese female patients who lost an average 6.2% of their body weight were observed to have a three-grade improvement in the severity of their papilloedema. A two-grade improvement was seen amongst five patients who lost an average of 4.3% and even the six patients in the study who lost only 3.3% showed an improvement by one grade. A significant correlation was found between grade change and percentage weight reduction (Spearman rank $p=0.002$). Sinclair et al (2009) showed that a mean weight reduction of 5.2% was associated with significant reductions in intracranial pressure in 20 patients with longstanding IIH. In addition, symptoms and signs of disease including headache and papilloedema showed significant improvement amongst the patients who lost weight.

No relationship between percentage weight reduction and Final Outcome was found in this pilot, in which mean weight loss overall was 4.6%, similar to that of both published studies. Furthermore, no significant trends were revealed when the effect of weight loss or gain upon the six components of IIH status was examined. This neither supports nor refutes the theory that weight loss in IIH is associated with improved clinical outcome, as the trial was underpowered to find such an association. The impact of weight loss in IIH warrants further investigation through specifically designed studies.

3.4.3.6 Pregnancies

There were five pregnancies in the study and changes in weight of the affected patients, where recorded, reflected this. Two of the pregnancies were terminated before the end of the study, but data was available on three patients in active pregnancy. One patient, allocated no acetazolamide, had a healthy delivery prior to the final trial visit and was asymptomatic at the end of the trial as well as at the visit preceding delivery, with no deterioration in her visual function observed during the pregnancy. Similarly, no worsening of the clinical features of IIH was seen in the two patients pregnant at the final visit, both in the second trimester. This is in keeping with the finding of Digre et al (1984) that outcome in IIH is the same for pregnant as non- pregnant patients.

The pregnancy rate in this study (10%) was perhaps surprising, given the stated exclusion criteria of pregnancy / planned pregnancy. There have been no well-documented reports or robust studies of the effects of acetazolamide upon pregnancy, (Lee et al., 2005) but the trial design reflected current practice of avoiding its use in pregnant patients due to concerns about the potential for congenital malformations.

In addition to the effect on protocol compliance, a high prevalence of pregnancy would affect the data collected on body weight. This was not a major concern with the current trial, since roughly equal numbers of patients from each allocation arm were affected, plus the study was not designed specifically to examine the effect of weight change. Future trials seeking to reduce the prevalence of pregnancies should screen carefully for women planning to become pregnant and emphasise the need for contraception.

3.4.3.7 Individual Outcome Measures

3.4.3.7.1. Symptoms

Headache prevalence amongst all patients fell from 70% at baseline to 54% at the final visit. Figures for transient visual obscurations, diplopia and visual loss also showed an overall reduction (64% to 10%, 22% to 2.5% and 26% to 5% respectively.) Tinnitus was unusual, in that the prevalence increased between baseline and final visits (56% to 58.5%, table 3.14). Some data inaccuracies were apparent, with tinnitus described as absent on the final status score yet recorded as present on the symptom checklist in four patients. Nevertheless, tinnitus was present in a surprisingly high proportion of patients who otherwise had marked reduction in their symptoms and the prevalence remained more or less constant from the start to the end of the trial period. Explanations could include significant inaccuracies in data collection, patients misinterpreting questions about tinnitus, or a high prevalence of intracranial noises due to causes other than IIH in this cohort. There are no published values for comparison. The study by Wall and George (1991) reported intracranial noises in 60% of 50 patients at the start of the prospective study, but no further prevalence data is provided.

3.4.3.7.2 Optic Disc Appearance

Papilloedema prevalence fell from 100% initially to 68% at the final visit across all patients in the trial according to the "is papilloedema present?" question on the examination documentation. Similarly, for the optic disc item on the final status score, 36.5% of all patients were recorded as having normal and 56% to have abnormal, stable discs, with just 7.5% have deteriorating discs. One patient had normal optic disc status, but papilloedema recorded as present and one other, papilloedema absent but optic disc status abnormal,

stable. Otherwise there were no discrepancies in the data. The majority of patients thus had papilloedema at the end of the trial, with abnormal, stable disc appearances. This is in keeping with the clinical observation that optic disc appearances continue to show chronic changes in patients with IIH.

Wall and George (1991) found a very similar reduction in papilloedema between the initial and final visits, from 100 to 64%. In the prospective study of 24 patients by Sorensen et al, (1988) complete resolution of papilloedema was seen in 50% after a combination of medical and, in some cases, surgical treatment, usually three to six months after the start of treatment. The remainder developed chronic papillary changes (42% of patients), optic atrophy (4%) or still had acute papilloedema (4%) at the end of the study.

There was no difference in papilloedema resolution between allocation arms at any time point and by repeated measures analysis. In the study by Celebisoy et al, (2007) papilloedema grades were reported to regress after a mean treatment period of 5.1 months in the 20 patients treated with acetazolamide and 5.1 months in the 20 treated with topiramate (no significant difference). No other published studies exist for comparison.

The treating clinician's assessment of optic disc status had strong concordance with final IIH outcome (D=0.59), second only to that of visual field status. This shows that the appearance of the optic disc had a greater influence on the clinician's assessment of disease status than most other signs or symptoms, as was expected from observation of current practice. The use of subjective assessment is entirely justified in this study, since no recognised, validated measures of IIH disease status exist and management decisions are routinely made in this manner. The results for the influence of optic disc status on final outcome highlight the need to develop more objective and reliable measures of papilloedema in IIH. Many studies

classify optic disc appearance according to scales, such as the Frisen (1982) grading scheme and this is discussed in more detail in chapter 4.

3.4.3.7.3 LogMAR acuity

No patient in either allocation had their final visual acuity status assessed as deteriorating and it was recorded as normal in 85%. Examination of recorded LogMAR visual acuities at each visit did not show any significant changes throughout the trial. Of the six clinical features examined for their influence upon final IIH outcome, visual acuity had the lowest concordance (D=0.05). Acuity was thus neither a useful nor sensitive measure of visual function in this study population.

Wall and George (1991) also found no significant change in Snellen acuity from initial to final visits and showed that acuity testing was not associated with visual loss found by perimetry or with papilloedema grade. In the Iowa long-term follow-up study by Shah et al, (2008) mean visual acuity remained stable over the period of the study, despite worsening of visual field being observed amongst some patients.

Orcutt et al (1984) combined visual acuity with visual field appearance in describing visual loss in 68 patients with 'benign intracranial hypertension'. A reduction in Snellen acuity of at least two lines, or a new field defect or field constriction of greater than 20% defined 'definite' visual function loss, whilst the term 'severe' was reserved for acuities worse than 6/60 or field constriction to less than 10 degrees with a 14e target on Goldmann perimetry. Although 49% of all eyes had definite loss of vision during the study over an average of 4.1 years, no eye lost acuity without a visual field defect. Detailed data on individual acuities was

not provided. Visual acuity was also found to be insensitive to visual loss found on perimetry in the prospective study of 35 patients by Rowe and Sarkies. (1998) Amongst 110 eye tests over 3 years, abnormal visual acuity was documented in 36 tests (33%) compared to abnormal visual fields in 103 tests (94%).

Whilst measurement of visual acuity is essential in clinical practice, its use as a trial outcome measure is limited by its sensitivity. Evidence suggests that patients observed to have deteriorating visual acuity will already have exhibited abnormalities on other tests of visual function. Visual acuity measures central visual function, reflecting retinal function in the central foveal area and does not indicate the condition of the peripheral or paracentral fields. Central vision is often spared in longstanding papilloedema, even in the presence of marked visual field abnormalities. More sensitive measures should be employed in studies where treatment effects may be small.

3.4.3.7.4 Visual Fields

At the final visit, visual fields were described as normal in 22 patients (58%), abnormal but stable in 16 (42%) and abnormal, deteriorating in none. There was a significant overall improvement in the MD values for both eyes when all patients were compared at baseline and at the final visit. Overall, 37% of the MD values at the final visit were determined by the perimeter software to be outside normal limits, compared to 74% at baseline. A learning effect is known to occur with perimetry, where improved performance is seen the more the tests are repeated. (Keltner et al., 2000) Most patients in this study completed three or more visual field tests, with 84% of patients completing all five scheduled examinations. It is

impossible to accurately assess the learning effect on the results and to reduce the impact of this in future studies would require tests to be repeated at each time point. Perimetry is time-consuming and requires specialist equipment and supervision, plus patients have to concentrate and tend to dislike the test, so this option is not always practicable. In this study, repeating the visual field tests was not felt to be in keeping with the pragmatic design. Only one other study has published perimetry MD values in IIH at more than one time point. The retrospective study by Bruce et al (2009) reported mean MD values amongst 422 women and 66 men at their first and last visits, and values appeared to improve in both groups, but neither the study duration nor the significance of the changes were supplied. Wall and George (1991) applied their own grading criteria to visual fields in their prospective study. They found that 60% of patients had improvement of Goldmann visual field grade and 50% had improvement of automated perimetry grade. The same grading system was used in the study by Rowe and Sarkies, (1998) in which 35 patients had at least two examinations over a three year period. Humphrey automated perimetry demonstrated abnormalities in 82% of patients at the first visit and 56% at the final visit. There was a significant improvement in the grade of visual field loss from first to last assessment. Celebisoy et al (2007) also used the grading system as the main criterion to assess clinical improvement in their study comparing acetazolamide and topiramate. When the visual field grades at the beginning of the study were compared with those at the end of the third, sixth and twelfth months a significant improvement was demonstrated. The effect of repeated testing upon the results was common to all three studies, with no specific measures employed by any to minimise its impact.

Treatment allocation was found to have no effect on any measure of visual field status in this study. As with all other results, this reflects the sample size and trial design and no published data exists for comparison. Whilst other studies have demonstrated the superiority of perimetry as a sensitive measure of visual function, there is as yet no literature on its sensitivity as an outcome measure for intervention trials. Visual field status was found in this study to have the strongest concordance with final outcome (Somer's D=0.66), suggesting that clinicians do rely most on the visual field appearance when judging IIH status. This should strengthen the argument for including visual field assessment in all future studies whilst striving to overcome the problem of the effect of learning upon the results.

3.4.3.7.5 Contrast Sensitivity

A mild improvement in contrast sensitivity was apparent throughout the study, in those patients for whom it was measured using Pelli Robson charts. As only 19 of the trial patients were tested and almost all of the values could be considered as falling within the normal range, further statistical analysis of the results is not warranted. The finding of an apparently significant result amongst the repeated measures analyses for right contrast sensitivity should be regarded as spurious.

Wall and George (1991) reported abnormal contrast sensitivity at the initial visit in 25 (50%) of 50 patients. Results were abnormal at the final visit in only 38% of the patients, although two patients who initially had normal contrast sensitivity had abnormal results at the end of the study. Interestingly, contrast sensitivity was the only visual parameter to correlate with the symptom of visual loss (p=0.02). Different methods were used to assess the contrast sensitivity, namely Arden gratings for the first two years, replaced by a Vistech contrast chart

for the final four years of the study. Rowe and Sarkies (1998) used Pelli Robson charts in their prospective study of 35 patients, reporting no difference between the sensitivities of contrast sensitivity and visual acuity, but data on the values recorded was not provided. The test was shown to be significantly less sensitive than visual field assessment. Other more technical methods of measurement may have greater sensitivity, but are likely to be less widely available and more time consuming for the patient. Pelli Robson charts have the advantages of simplicity and low cost to recommend their use, but seem unlikely to enhance trials in which accurate assessment of visual field defects is undertaken.

3.4.3.7.6 Health-related quality of life data

The use of standardised questionnaires provided health-related quality of life data at three time points during the study. The SF-36 produced eight scores between 0 and 100, measuring three aspects of health: functional status, wellbeing and overall evaluation of health. In addition to the eight scales, change in health was measured by a single question in the questionnaire, in which patients were asked "Compared to three months ago, how would you rate your health in general now?" and required to choose one of five responses "much better", "somewhat better", "about the same", ""much worse" and "somewhat worse."

There is one published study of SF-36 subscale scores in IIH. Using questionnaires at a single time point, Kleinschmidt et al (2000) demonstrated significantly lower (worse) scores amongst 28 women with IIH for all eight measures of the SF36 except energy/vitality, role-emotional and mental health when compared to 30 age- and weight-matched as well as 30 age-matched, normal weight, female controls. The values from this study are compared with

the mean values amongst the IIH trial patients, as well as published normal values from two adult population studies in table 3.23. Although statistical testing of the data is not possible, the scores from the Kleinschmidt study appear worse across all of the eight scales. Values from the IIH trial appear closer to the normal scores from population studies, with the possible exceptions of pain and general health. This may reflect differences in the characteristics of the patients in the two studies, as those in the Kleinschmidt study were at various stages in their IIH disease and had a variety of co-morbidities. A more recent study by Daniels et al (2007) showed that 34 patients with IIH had lower scores for SF-36 Physical Components Summary ($p<0.0001$) and Mental Components Summary ($p<0.0001$) compared with United States norms for females, as well as with 41 patients with neuro-ophthalmological disorders ($p=0.02$, Physical Components Summary only.) There are no other published studies of SF-36 in IIH. The finding of near-normal scores for many patients in this pilot is perhaps surprising, but is consistent with other results suggesting that patients with less severe IIH were enrolled.

Table 3.23 Mean SF-36 scores amongst all IIH patients at baseline and mean scores from three published studies. *Scores are estimated to nearest 0.5 from published bar chart

	IIH Trial Baseline visit n=48	*IIH patients US case-control study* (Kleinschmidt) n=28*	*UK General population (Garratt, 1993) n=542*	*US general population (Ware, 1994) n=2,474*
Physical Function	**79.9**	57.5	79.2	84.2
Role-Physical	**69.5**	35.0	76.5	80.9
Role-Emotional	**77.2**	46.5	75.0	81.3
Social Function	**70.3**	51.5	78.6	83.3
Mental Health	**64.4**	56.5	73.7	74.7
Energy Vitality	**51.6**	29.5	61.2	60.9
Pain	**57.8**	41.5	76.9	75.2
General Health	**57.6**	40.0	68.7	71.9

When baseline scores for all patients were compared with those at the end of the study, the only observed differences were for SF-36 subscales pain and change in health. Mean score for pain improved from 57.8 to 77.8 (p=0.02). This is compatible with the clinical data for headache incidence, which improved from 70% to 54% overall, but it should be noted that the term pain in this questionnaire is specified as bodily pain, rather than headache. The mean score for change in health improved from 47.8 at baseline to 59.7 at 12-months (p=0.01). Thus more patients at the end of the study reported their overall health as better than three months ago than when the same question was posed at the start. It is possible that the time limit of three months for this question (rather than one year as used in other versions of the SF-36) reduces the relevance of the finding. Had the question addressed overall health as compared with one year previously, an even greater improvement may have been seen at the final visit. This should be considered in the design of future studies.

There was little evidence of mood disturbance in this pilot. HADS scores for most of the patients fell within the normal range for anxiety and depression (0-7). At each visit and in each allocation arm, very few patients showed scores in the borderline or abnormal categories, as shown in table 3.18. Anxiety was more commonly reported than depression overall. Throughout the study, approximately one quarter of patients had scores indicative of abnormal levels of anxiety (score range 11-21, mean 23.2% of patients). At baseline, the mean score amongst all patients for anxiety (7.42) fell just outside the normal range, whilst for depression (4.19) it was clearly normal. By the end of the study, all mean scores were within the normal range, although the improvement was not significant. Furthermore, repeated measures analysis showed no differences between the allocation arms and no

significant trend was observed when numbers of scores in each category were compared over time.

In the study by Kleinschmidt et al, (2000) depression scores on the Beck Depression Inventory and anxiety scores on the Spielberger State-Trait Inventory were found to be higher (worse) in IIH patients than the normal weight controls ($p<0.002$ and $p<0.015$ respectively) but not significantly different to weight-matched controls. No studies have examined the change in mood scores before and after treatment in IIH. There is a wealth of literature linking obesity and mental health and since all except two of the patients in this pilot were overweight, it is not possible to speculate about the effect of this on the assessment of their mental state.

The EuroQol scoring systems (visual analogue and EQ-5D) were also not sensitive to change in this study. There was no improvement in scores overall from baseline to final visit, nor were any differences observed between the allocation arms. There are no reports at all of the use of EuroQol scores in IIH in the literature. Its inclusion in a pilot study such as this is justified on the grounds of its simplicity to administer and the potential to generate a single index value for health status. It was designed to complement other instruments and may have a role in future IIH studies in which the overall health of patients is more adversely affected by the disease.

Of the three measures used in this pilot, the SF-36 appears to be the most appropriate, based on the observed improvement from the start to the finish of the trial in two of the subscales. Care is required in the interpretation of the scores when, as in this study, the 0-100 scoring algorithm is used (based on the summated rating method), rather than the more recently introduced norm-based algorithm. The shapes of the profiles in figures 3.12 and

3.13 reflect both the impact of IIH on SF-36 health concepts as well as arbitrary differences in ceilings and floors of the SF-36 scales. (Ware et al., 2000) Thus the average score for each scale differs substantially across the profile for reasons other than IIH. It is not correct, for example, to infer from the profile in figures 3.12 and 3.13 that IIH has a greater impact on energy / vitality and general health than physical function. The use of the newer, norm-based scoring method, in which below-average health status is indicated by a scale score below 50 and differences in scores more clearly reflect the impact of the disease, should be adopted by future trials.

As no published studies have measured health-related quality of life before and after intervention in IIH, there is very little to guide which scales should be used when planning trials. The levels of anxiety reported in this study should not be ignored, despite the lack of observed changes with time or treatment. Certainly, some measure of mood, functioning and quality of life would seem to be important when studying the impact of IIH, particularly if a goal of future trials is to recruit patients with more severe disease and higher overall morbidity.

3.4.3.8 Composite Outcome

The use of a combination of commonly measured variables as an overall clinical assessment tool for IIH was explored by this study. This was based on the observation that decision making in IIH seems to depend upon the consideration of various components of the clinical assessment, with varying amounts of importance apparently being attached to each. As with many conditions and with clinical reasoning on the whole, subjective judgement by experienced clinicians forms the mainstay of management. Objective, reproducible, sensitive

and standardised measures to guide this process have obvious potential benefits and are essential to the design of future trials. The quest for such measures begins with an assessment of how clinical judgement is influenced.

Data from the analysis of the six items for which final status was assessed by the clinician provided valuable information to guide the creation of a composite scoring system. Visual acuity had the least influence on the final IIH status and appears to be a poor measure of disease activity. The presence of symptoms such as headache, tinnitus and visual obscurations also appeared to add little to the evaluation of disease severity. The data suggests that perimetry and appearance of the optic disc are the most influential measures, as shown by their strong concordance with IIH status (Somer's D 0.66 and 0.59 respectively).

Combining the examination of optic discs with the perimetry findings seems to be the most appropriate and sensitive method of routine disease assessment and has been recommended as such in several publications. (Orcutt et al., 1984; Wall and George, 1991; Rowe and Sarkies, 1998) In future, newer techniques such as computerised optical coherence tomography may have a role, but remain to be formally evaluated and are not currently widely available. It would seem sensible therefore to prioritise visual field assessment and optic disc appearance in any composite measure of IIH. This leads to the concept of weighting the various components of the measure to reflect their apparent importance, with visual fields and optic disc being obvious candidates to have higher scores attached.

In the scoring system piloted by this study, the theoretical maximum (worst) score was 12, since each of the six components scored 0, 1 or 2 according to subjectively judged severity and all six contributed equally to the final score. The mean value for all 50 patients at the

final visit was 2.75 (2.6 in the acetazolamide group and 2.9 in the control group, no significant difference.) Further development of composite scores could include a wider choice of scoring options for those components with greater influence upon overall disease status. Grading systems for visual field and optic disc abnormalities have been adopted by several major published IIH studies, (Wall and George, 1991; Rowe and Sarkies, 1998) with greater than three possible grades for each parameter. Further studies could combine higher total possible scores for these measures with more limited ranges for disease features such as acuity and headache, to reflect their differing impact on the overall disease.

One further theoretical problem with the scoring system in this study is the heterogeneity of its components. It includes markers of active disease (papilloedema, obscurations) as well as measures of damage that may be present whether or not the disease is still active (field defects, acuity). In addition, measures are included that may indicate either active disease or alternative pathology (headache, tinnitus). The assignment of lower maximum scores to some components, notably headache, would to some extent resolve this issue. Furthermore, the score in this pilot was calculated for a single time point, so no comment about the behaviour of the scoring system over time is possible. It would seem sensible in future to examine the longitudinal behaviour of the composite score, by repeating its measurement at multiple time points. This may also address some of the problems associated with the inclusion of such heterogeneous measures.

3.5 Summary

This is the largest trial and the only randomised controlled trial in IIH to date. 50 patients were recruited from five centres over a 23 month period. Patients had the typical

characteristics of IIH, being predominantly obese, young females with headache as their most common symptom. Recruited subjects appeared to have a mild form of IIH and there was a low incidence of visual dysfunction at the start of and throughout the study. The overall dropout rate was 20%, but protocol non-compliance was seen in 16 patients (32%).

Most patients experienced improvement of their disease, with 44% judged to have IIH in remission at the end of the trial and significant improvement in symptom prevalence, optic disc appearance and visual fields. No differences were seen between subjects allocated to receive acetazolamide and those allocated no medication when outcomes were compared at baseline and final visits or by repeated measures analysis, although the trial was underpowered to detect a treatment effect. The only quality of life measures reflecting improvement were the pain and change in health subscales of the SF-36. No patient had blinding visual loss, surgical intervention was required in just two patients and there were five pregnancies during the study. Most patients lost weight during the trial, with a mean loss overall of 4.6%.

A scoring system based on common clinical features of IIH was tested and used to create a novel composite outcome measure. Visual fields and optic disc appearance had the greatest influence on IIH disease status and are the most important components of the clinical assessment. Future studies should incorporate weighting into composite scores to reflect this.

Difficulties of recruitment and compliance with treatment have been highlighted by this study. In addition, a tendency to recruit only those patients with benign forms of the disease was observed. Future trials need to address these issues for meaningful conclusions to be drawn whilst maintaining a sufficiently pragmatic overall design.

CHAPTER 4

THE ASSESSMENT OF PAPILLOEDEMA IN IIH

4.1 Background

Papilloedema, swelling of the first part of the optic nerve (the optic disc or papilla) in the presence of raised intracranial pressure, is almost a universal clinical finding in IIH. In the assessment of both newly diagnosed and more longstanding IIH, the appearance of the optic disc is a key measure of disease status and the effect of treatment. In addition to the presence or absence of papilloedema, the degree, severity and chronicity of the disc swelling is important to determine.

4.1.1 Papilloedema classification

Attempts have been made to grade and classify disc swelling. 'The Ocular Fundus in Neurologic Disease: a Diagnostic Manual and Stereo Atlas' (St Louis, CV Mosby, 1966) published in 1966 by neuro-ophthalmologist, William F Hoyt and photographer Diane Beeston, contained a classification of stages of papilloedema described as early, fully developed, chronic and atrophic, with serial photographic documentation of examples of evolving disc oedema. The book sold out almost immediately but was never reprinted. In 1969, the Neuro-Ophthalmologist Michael Sanders published a similar temporal classification based on a fluorescein angiographic study of 69 cases, dividing papilloedema into five groups according to an estimation of its duration.(Sanders, 1970) All cases were under investigation at the National Hospital in London and all had elevated CSF opening pressure at lumbar puncture. Diagnoses were stated for 42 of the cases, as 'Benign

Intracranial Hypertension' (22), malignant tumours (13) and meningioma (7). The five groups were termed early, acute, chronic, vintage and atrophic and detailed descriptions of the features in each as well as the approximate times since onset of the process were provided, as summarised in table 4.1.

Table 4.1 A summary of Sanders' descriptive classification of papilloedema (Sanders, 1970)

Group	Duration	Main features	Angiographic features
Early	Hours/ days	Hyperaemia of disc Blurring of disc margins Full tortuous veins, absent pulsation Grey colour of peripapillary retina above / below disc (oedema in nerve fibre layer)	Allows dilated vessels on disc to be seen (may extend to retina) Leakage of dye mainly above and below disc (increased vessel permeability), seen as residual fluorescence
Acute	Days / weeks	Fully developed papilloedema Retinal veins elevated by disc swelling Arteries often obscured Haemorrhages- superficial (nerve fibre layer), deeper, punctuate or more extensive, in sub-hyaloid space White areas- probable cotton wool spots or resolving haemorrhage	Consistent with ophthalmoscopic appearance Striking appearances in residual photographs Early filling of disc capillaries is followed by extensive leakage(dye spread widely into surrounding retina along nerve fibres)
Chronic	Weeks / months	Less active picture Few haemorrhages / exudates Marked vascular network on surface of disc Underlying contrasting grey glial reaction often seen	Demonstrates maximal disturbance often in peri-papillary plexus Micro-aneurysms frequent Massive leakage of dye
Vintage	Months / years	Multiple small drusen-like bodies on disc surface May see optociliary shunt vessels	Early filling of optociliary or shunt vessels during arteriel phase Venous study may demonstrate surrounding choroidal degeneration
Atrophic	Years	Optic disc pallor Peri-papillary choroidal degenerative changes visible	Marked attenuation of retinal arteries, with few branches No leakage of dye

Sanders claimed that the category of acute papilloedema is simplest to diagnose due to the increase in signs from the early stage and the appearance of haemorrhages and exudates.

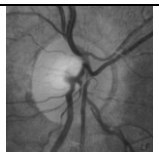
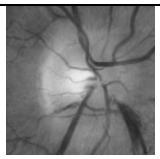
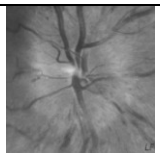
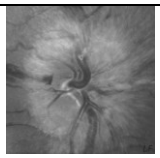
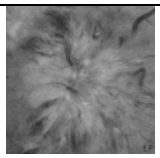
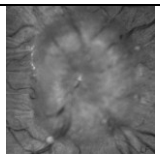
Greater difficulties arise with the diagnosis of early papilloedema, where several factors may influence the disc appearances at the time of examination, such as fluctuations in CSF, intra-ocular or systemic blood pressures, so that angiographic demonstration of disc capillaries and leakage may be essential. The exact aetiology of the vascular changes seen in chronic papilloedema is not known, although it is suggested that they result from compensatory mechanisms to overcome disordered pressure and perfusion gradients in the region. More prolonged elevation of pressure can induce the degenerative changes seen in the 'vintage' variant of papilloedema. Here, as in the three previous groups, many features are reversible, unlike the fifth or 'atrophic' stage in which disc pallor is permanent and visual loss has occurred.

The division of the various optic disc appearances into the five categories was entirely arbitrary and focussed principally on providing descriptions of the progressive development of papilloedema. The publication was designed to aid the ophthalmologist in judging the duration of a particular case of papilloedema and the possibility of visual failure.

More recently, Lars Frisen (1982) published a numerical scheme describing stages of swelling of the optic nerve head according to various components of the ophthalmoscopic picture. The original paper reported the grading of 78 fundus photographs showing either normal discs or acquired disc swelling of various aetiologies, by three clinicians blinded to clinical information. The published paper included black and white photographic examples and descriptions of six distinct grades, summarised in table 4.2. The aim of the scheme was to provide a detailed terminology for the various components of the ophthalmoscopic appearance and facilitate the identification of a change in swelling in the individual case. Increasingly pronounced changes are seen at successive stages and short-term fluctuations

in appearances are said to be accommodated by sufficiently large intervals between stages of the scheme. Stages 1 and 2 represent early disc swelling, stage 3, moderate abnormality, stage 4, severe and stage 5, a transitional stage towards progressive atrophy.

Table 4.2 Summary of the Frisen Staging Scheme (Frisen, 1982)

Stage	Summary of ophthalmoscopic features	Example
0	Normal disc Radial pattern of peripapillary nerve fibre bundles	
1	Disruption of the normal radial arrangement of the nerve fibre bundles Excessive blurring of the nasal disc border -subtle grayish halo Sparing of the temporal margin – temporal gap in halo	
2	Halo surrounds the disc Nasal margin is elevated Concentric or radiating retinochoroidal folds may be seen	
3	Additional elevation of the temporal margin, clearly enlarged disc diameter One or more segments of major retinal vessels obscured by elevated disc borders Irregular, fringed 'circumpapillary halo' with finger-like extensions	
4	Elevation of the entire nerve head Total obscuration of a central retinal artery or vein, *or* Optic cup compressed to a slit or completely obliterated	
5	Dome-shaped appearance of the nerve head - dominance of anterior over sideways expansion Halo is narrow and smoothly demarcated Some obscuration of vessels as they climb steeply over the dome	

Frisen highlights the major role of axonal swelling in the production of papilloedema, seemingly a consequence of locally arrested axoplasmic transport. Difficulties in recognising early changes within the disc itself are acknowledged, such that the early stages of the scheme refer to changes at the disc border, whilst more advanced stages reflect anterior expansion of the swelling nerve. The proposed scheme is applicable to a large variety of

conditions, except swelling of the optic nerve head by 'elements normally foreign to the area (for example neoplastic cells)' and is not specific for raised intracranial pressure. Any vascular components, such as venous stasis, hyperaemia, haemorrhages and infarcts are disregarded on the basis that various pathogeneses and 'individual peculiarities' lead to considerable variety of expression of such features.

The results of an attempt to assess the reproducibility of the Frisen scheme were published alongside its original description. The 78 slides under scrutiny comprised one fundus photograph from each of 12 subjects with normal discs, 12 with disc abnormalities 'reminiscent of acquired disc swelling' and 54 subjects with differing degrees of acquired disc swelling of known aetiology. No further diagnostic information was provided. The author plus an ophthalmology resident and a medical student assigned a stage number to each of the photographs, as they were projected in random order as slides with a uniform degree of magnification, without access to clinical information. The exercise was repeated by all, a minimum of four weeks later. The assigned scores were identical on re-test for 80% of the slides assessed by the two senior observers and 75% for the medical student. Between examiners, there was exact agreement for 49% of the slides and a difference of only one unit for 86%. For the three observers, 88 to 96% of normal discs were correctly classified and the fraction of abnormal discs correctly identified ranged from 93 to 100%.

Anomalies of otherwise normal optic discs, resembling swelling, were the cause of most difficulties for the junior observer. Concentrating on axonal swelling as the most important element of papilloedema was regarded by Frisen as more reliable than using other indicators of disc swelling, such as the presence or absence of venous pulsations and ophthalmoscopic measurement of disc protrusion. It was proposed that this focus of the scheme on fine

details would aid the differentiation of papilloedema from innocuous normal variants, although it would not, nor was it intended to discriminate between the various aetiologies of disc swelling.

Not only is the Frisen scheme applicable to a wide variety of pathologies besides IIH, but vascular changes, which may have clinical significance in IIH, are not included. Furthermore, the successive stages of Frisen's scheme reflect increasing abnormalities as the degree of optic nerve swelling worsens; no indication is given as to how the scheme can be applied to the process in reverse, as papilloedema resolves. Unlike the Sanders classification, the Frisen scheme makes no attempt to judge the duration of the swelling. Patients with IIH frequently present with papilloedema over long periods of time, thus some measure of the chronicity of their disc swelling is desirable.

4.1.2 Papilloedema grading in IIH Literature

Despite its apparent limitations, the Frisen scheme, or some variant thereof, is frequently reported as a major outcome measure in published case series, analyses and trials in IIH. Some have also referred to the Sanders classification. Examples are given in table 4.3.

Many early publications refer simply to the presence or absence of papilloedema when describing the clinical course of IIH. More recently, studies have provided greater detail regarding the severity or duration of disc swelling, particularly in relation to cases of IIH in which visual loss has occurred. Corbett et al (1982) described the persistence of papilloedema in nine of 57 patients five to 13 years after their initial symptoms, three of whom had severe visual loss as measured by acuity and perimetry. In addition, choroidal retinal folds were reported in six patients with persistently enlarged blind spots. Optociliary

Table 4.3 Examples of major studies in IIH with assessment of papilloedema as a key feature

Year	1st Author	Type of study	n	Assessment of Papilloedema
2009	Bruce	Retrospective review	658	Systematic review of fundus photography Median Frisen grade at first and last visit
2008	Shah	Retrospective review	20	Frisen grading of stereo optic disc photographs Consensus of three independent observers Median grades at initial and final visits
2007	Celebisoy	Prospective open-label study	40	Grading of papilloedema at ophthalmoscopy Frisen grades reported for initial visit only
1998	Kupersmith	Retrospective review	58	Modified Frisen grading Mean grade as main outcome measure
1998	Johnson	Retrospective review	15	Novel Frisen-based grading of stereoscopic slides Consensus of three observers Masked review against investigators 'gold standard'
1991	Wall	Prospective study	50	Frisen Grade Average optic cup size ratio
1988	Sorensen	Prospective study	24	Optic disc appearance described as normal, oedema / gliosis, or atrophy Disc protrusion measured in dioptres
1984	Orcutt	Retrospective review	68	Sanders classification Degree of disc elevation graded as low or high grade
1982	Corbett	Retrospective review	57	Absence/persistence of papilloedema on photographs Descriptions of features in specific cases

collateral vessels were seen in three cases and, amongst patients whose papilloedema subsided, several features were described as sequelae of the prior disc swelling, such as gliosis of the disc and circumpapillary pigmentation. Two years later, Orcutt et al (1984) published a study of factors affecting visual loss in 'Benign Intracranial Hypertension' in which the co-author Sanders' own classification was applied to stereoscopic fundus photographs from 68 patients. The chronicity of disc swelling was not seen to correlate with visual loss, with no significant relationship of visual deterioration with acute, chronic or vintage papillodema. However, the degree of oedema was also graded according to the actual elevation of the disc, as 'low' or high' grade, where the latter had greater than 4 dioptres of swelling measured ophthalmoscopically and this was found to be associated with poor visual outcome.

Sorensen et al (1988) also measured the degree of disc swelling in IIH. In a prospective study of 24 patients, ophthalmoscopy and colour fundus photography were used to subjectively evaluate the disc appearance as well as record the disc protrusion in dioptres. The evolution of changes throughout a mean of 49 months was observed. Initially all patients had papilloedema described as acute, which resolved completely in 50%. Development of chronic papillary changes was reported with gliosis of the optic discs in 42% of patients. One patient developed optic nerve atrophy. Patients with complete resolution of their papilloedema showed a rapid decrease in disc protrusion within the first months of treatment.

The prospective study by Wall and George (1991) was the first major publication to report the use of the Frisen scheme to assess outcome in IIH. 50 patients, examined at least twice over an average follow up of 12.4 months, had the Frisen grade recorded at all visits following ophthalmoscopic examination. Stereoscopic photographs were taken at the initial visit and again whenever change occurred. In addition the average optic cup size ratio was measured, as vertical cup diameter: total vertical disc diameter, although comment was made that measurement was difficult when discs were elevated. The authors found a significant improvement in papilloedema grade in both eyes and a significant change in cup size ratio, in the left eye but not the right, from the initial to the final visit. Interestingly, neither papilloedema grade nor final cup size correlated with other measures of visual loss in the study.

Kupersmith et al (1998a) used a slightly modified version of the Frisen scheme to retrospectively compare papilloedema in 58 patients with and without weight loss; only grades 0, 1, 3 and 5 were employed at one of two centres in the study. Grade 0 was assigned

to cases in which the papilloedema resolved. The mean grades for the worst eyes in each subject, as well as for both eyes, were reported for the initial visits and six months or more after baseline. A mean time to improve one grade in papilloedema of 4.0 months for 38 patients who lost weight compared to 6.7 months for 20 patients with no weight loss was cited as evidence of the beneficial effect of weight reduction in IIH.

In the same year, Johnson et al (1998) used a modified version of the Frisen scheme in a study of 15 patients, also aiming to assess the association of weight loss with resolution of papilloedema in IIH. Stereoscopic slides of the optic disc from the eye with the more advanced papilloedema from each patient were reviewed in a masked fashion by three of the authors and assigned a grade by comparison against 'gold standard' photographic examples. The gold standards were photographs from earlier studies for which there was complete agreement about the grades amongst the authors as well as by three senior neuro-ophthalmologists with expertise in optic disc evaluation who had graded them previously. Four grades (0=absent; 1=mild; 2=moderate and 3=marked) described the severity of papilloedema. Thus the maximal change in the study was three-grade change (optic disc oedema changing from marked to absent). Grade 0 was equivalent to Frisen Stage 0, grade 1 to Frisen stages 1 and 2, grade 2 corresponded to Frisen stage 3 and grade 3 to Frisen stages 4 and 5, with vascular changes disregarded in both schemes. The results of this study, including a mean weight loss of 6.2% amongst 10 patients with complete resolution of papilloedema and a significant correlation between percent weight lost and the papilloedema grade change, provided further support for the role of weight reduction in IIH.

More recently, three papers have adopted the Frisen scheme as their sole measure of papilloedema in IIH. Celebisoy et al (2007) reported grades of 3, 4 or 5 amongst all of 40

patients at the initial visit of a treatment trial comparing acetazolamide with topiramate. Visual field grades were chosen as the main outcome for the study and no subsequent Frisen grades were reported in the results, although the mean treatment period before regression of papilloedema grades was quoted for each group. Shah et al (2008) used the mean Frisen grade, determined by a consensus of three independent neuro-ophthalmolgists' evaluations of stereo disc photography, to illustrate the occurrence of delayed worsening in IIH during a ten year observation period, although they too opted for visual field defects and not papilloedema as the primary visual outcome. Most recently, Bruce et al (2009) systematically assessed disc photographs from over 600 patients with IIH and assigned a Frisen grade at the initial and last visits in a review spanning 18 years in three US centres. Whilst this study also omitted papilloedema grade as a major outcome measure, its use illustrates the increasing trend in IIH literature for including the Frisen scheme in its original, unmodified form.

4.1.3 Evaluation of the Frisen Staging Scheme

Using all combinations of the search terms "Frisen staging scheme", "papilloedema classification", "papilloedema grading" and "optic disc swelling" a formal search of all major online scientific databases was carried out. With the exception of the original paper, (Frisen, 1982) there are no publications reporting the systematic assessment of the clinimetrics of the Frisen staging scheme. The high sensitivity (93-100%) and specificity (88-96%) values published by Frisen probably reflect the broad range of diagnoses in the study as well as the role of the author himself as one of the graders. Despite this, the scheme is now widely employed as a measure of papilloedema. Some studies report attempts to substantiate its

use through the inclusion of more than one observer to assign the staging, but these are in the minority.

In a study examining the use of optical coherence tomography in papilloedema, Karam and Hedges (2005) used a modified version of the Frisen scheme to grade optic disc swelling in 32 patients with mild papilloedema or congenitally crowded optic nerves and 17 normal subjects. Two observers, masked to patient histories, reviewed colour and red-free photographs after they were mixed and shown randomly, and identified each disc as either normal, congenitally crowded or papilloedematous. For the latter group, they assigned grades of disc swelling as normal or stages 0,1,2,3 or 4, according to descriptions provided. There was agreement over the identification of normal, crowded disc or papilloedema in 68% (71 photographs). As in the original Frisen paper, most of the differences occurred in the differential diagnosis of crowded disc versus papilloedema. Agreement by stage of optic disc swelling was just 62% (64 photographs). Despite the observers reportedly having experience in the evaluation of optic discs, there was thus considerable inter-rater variability when applying a slightly modified Frisen classification. Furthermore, the study included fewer stages in total than the Frisen scheme. Stage 4 included all discs with more than moderate papilloedema, defined as 'obvious, well established papilloedema with haemorrhages and exudates' - additional features that are disregarded by the Frisen classification. The stage was therefore broader, encompassing a wider range of abnormalities than the original Frisen stages and should, in theory, have been easier for raters to reach agreement about.

Not only has the Frisen scheme never been formally tested, the evaluation of optic disc appearances in IIH in general has not been subject to rigorous examination. Whilst the

importance of papilloedema in the clinical assessment of IIH is widely accepted, the determination of improvement or deterioration in papilloedema is usually the individual judgement of a sole clinician. Some measure of the variability of this subjective assessment would be of benefit, particularly in the interpretation of data from those studies in IIH with optic disc appearance as a key feature.

4.2 Preliminary study of inter-rater variability in the assessment of papilloedema

A pilot study was carried out in 2008, comparing the opinions of two consultant neuro-ophthalmologists in the evaluation of papilloedema in IIH. The aim of the exercise was to investigate the feasibility of a larger study and to provide some indication of the inter-observer variability that could be expected when photographs of a cohort of patients with IIH were assessed.

4.2.1 Methods

A selection of optic disc photographs from the patients enrolled in the IIH Trial Pilot was used for this study. Sets of two, three or four disc photographs were included, to give a total of 42 photographs from 12 patients. Within every set, each photograph showed the same eye (right or left) taken at a different time point in the trial.

Photographs were labelled “Xn”, where X = patient identified by letter from A to R and n = number in sequence, i.e. 1, 2, 3 or 4. Although photographs were taken from patients at successive visits for the IIH Trial Pilot and were stored in chronological order, for the purpose

of this study they were presented to the raters in an order defined using a computer-generated random list.

Two senior neuro-ophthalmologists, with expertise in the assessment of optic discs as well as in the management of IIH, independently rated the photographs. Images were coded as above and presented as JPG files, viewed using Windows Photo Gallery© (Microsoft Corporation). The raters, who had no access to clinical information about the patients, were asked to consider two questions:

1. Is there papilloedema - yes or no?
2. For each set of photographs, in the order they are presented, is each disc better or worse than the preceding disc in terms of papilloedema severity?

4.2.2 Results

For question 1, a total of 42 discs were assessed by each rater for the presence of absence of papilloedema. The results of each assessment were then compared. Disagreement between the raters occurred in seven of the 42 comparisons. In two of these cases, the answer 'possible' was given by one of the raters and 'no' (no papilloedema) by the other. The results are summarised in Table 4.4.

For question 2, a total of 24 comparisons were made by the two raters. In eight out of 24 cases there was disagreement between the raters as to whether the appearance of the disc was better or worse than the previous one. In two of these cases, one rater had assessed the disc as the same as the previous one. The results are shown in Table 4.5.

Table 4.4: Assessment of presence or absence of papilloedema
Occurrences of disagreement between the two raters are highlighted in yellow

Code → ↓	1	2	3	4	No. of comparisons
	Papilloedema yes (Y) or no (N) (Responses of rater 1 in blue, rater 2 in green)				
A	Y Y	Y Y	Y Y	Y Y	**4**
B	Y Y	Y Y	Y Y	Y Y	**4**
C	Y Y	Y Y	Y Y	Y Y	**4**
D	N Y	Y Y	Y Y		**3**
E	Y Y	N N	Y POSS	Y Y	**4**
G	N N	Y Y	N N	Y N	**3**
J	Y Y	Y Y	Y Y		**3**
K	Y Y	Y Y	Y Y	Y Y	**4**
L	Y N	Y Y	Y Y	 N	**3**
M	Y Y	N Y	N POSS	Y Y	**4**
P	Y Y	N Y	Y Y		**3**
R	Y Y	Y Y			**3**
				TOTAL	**42**

Table 4.5 Comparisons of papilloedema in successive disc photographs

Code → ↓	1	2	3	No. of comparisons
	Appearance worse (W) or better (B)? (Responses of rater 1 in blue, rater 2 in green)			
B	B B	W W	W W	3
D	W W	B SAME		2
E	B B	W B	B B	3
H	W W	B W		2
J	W B	B B		2
K	W W	B W	B B	3
L	B W	W W	B SAME	3
M	B B	B B	W B	3
P	B B	W W		2
R	B B			1
			TOTAL	24

In the first part of the exercise, the presence or absence of papilloedema, there was a crude rate of 85.7% agreement between the two raters. In the second part, the rate of agreement over the assessment of papilloedema as worse or better was only 66.7%. Thus in one third of cases, there was discrepancy between the two raters.

4.2.3 Discussion

This small scale pilot demonstrates the importance of considering inter-rater reliability in the assessment of papilloedema in IIH. In a simple exercise in which two senior neuro-ophthalmologists, from the same UK specialist centre, were presented with sets of disc photographs from a cohort of patients with IIH under identical conditions, rates of disagreement reached 33%. Whilst interpretation of the results of this exercise is limited by the small sample size, low number of raters and lack of a repeat assessment to exclude intra-rater variability, the findings raise questions regarding the methods of papilloedema grading used in larger studies.

There was greater agreement over the presence or absence of papilloedema (85.7%) than the determination of papilloedema status as better or worse (66.7%). It would seem reasonable from this finding to predict even greater levels of inter-rater variability in the assignment of grades of papilloedema, such as those described in the Frisen scheme, for which there are six possible options.

Since the Frisen scheme appears currently to be the favoured method for describing papilloedema in world IIH literature, further assessment of its performance as a measure in the condition is warranted.

4.3 Assessment of Papilloedema and the Frisen Scheme in IIH: The Blinded Disc Rating Study

In an attempt to shed further light on the applicability of the Frisen scheme for grading papilloedema in patients with IIH, a study of 'blinded rating' of a collection of disc photographs was conducted. The aim of the study was to estimate the inter-rater reliability of the Frisen scheme and investigate its use when comparing the papilloedema of IIH at different points in the clinical course of the disease. The sensitivity of the Frisen grading in IIH was explored. The hypothesis that changes in disc appearance could be recognised between discs assigned the same Frisen grade was tested.

4.3.1 Methods

Disc photographs were collected from 25 patients with newly diagnosed (acute) IIH and 22 patients with chronic IIH. Photographs were collected at two time points from each participant. In the case of the newly diagnosed IIH patients, photographs were collected on entry to and at the final 12-month visit of the IIH Trial Pilot. The chronic IIH patient cohort had photographs taken prior to and upon completion of a three month period of an intensive very low calorie total meal replacement diet, as part of a prospective evaluation of the effect of weight loss in IIH.(Sinclair et al., 2009) Thus, a participant had optic disc photography before and after a period of therapeutic intervention for IIH. Photographs were taken within the same ophthalmology department using the same equipment. All patients had pupils dilated.

All photographs were assigned a computer-generated, random numerical code known only to the investigators. Photographs of each eye from each patient, before and after treatment,

were kept in pairs, in folders also assigned random numerical codes. The folders were then arranged in a random sequence. The 'blinded rating' was performed by clinicians with expertise in optic disc evaluation: three consultants and one fellow in neuro-ophthalmology and two consultant neurologists with special interest in neuro-ophthalmology. The six observers, blinded to the identity of the patient and all clinical information, examined the paired photographs using Windows Photo Gallery© (Microsoft Corporation), on separate occasions and without conferring. The status of the therapeutic intervention (before or after intervention) was also masked for each photograph. Each observer assigned a Frisen grade to each disc photograph, using guidance from standard descriptions and photographic examples. In addition, observers were asked to compare the severity of papilloedema between pairs of photographs. For each pair, observers were asked to state which one showed the least severe disc swelling, or whether they appeared the same. This produced a ranking of the appearance of the discs in each pair.

To examine the agreement between observers, results of the Frisen grading were analysed for all possible pairings of the six observers, totalling 15 possible combinations of observers. This permitted calculation of probabilities of the assigned Frisen grades being the same, or differing by one, two, three, four or five grades.

The results of ranking pairs of discs were analysed in a similar way. The rankings from two observers on any given pair of disc were compared and three codes assigned to the result as follows: Code "0" if both observers gave the same result, code "1" if one observer assessed the photographs as the same, but the other observer ranked one as showing less papilloedema than the other and code "2" if both observers ranked the photographs differently (one observer chose one photograph as showing the least papilloedema and one

chose the other photograph). This can be summarised as: 0 = both observers agree, 1 = 'minor' disagreement, 2 = 'maximum disagreement'. By analysing the results in this way for all possible combination of pairs of observers, probabilities for each code were calculated.

The assigned Frisen grades were then compared to the ranking for each pair of photographs, to explore the agreement between the two methods. For this, all photographs were analysed in the same chronological order. Assigned Frisen grades were examined for each pair and coded as "F0" if the first photograph had the lower Frisen grade, "F1" if both photographs had the same Frisen grade or "F2" if the second photograph had the lower Frisen grade. A similar code was applied to the ranking data, (code "R0" if the first photograph of the pair was ranked as having less severe papilloedema, "R1" if photographs were judged to be the same and "R2" if the second photograph was ranked as having the less severe papilloedema.) The coding systems were compared and a final 'agreement' code applied to each pair of photographs, where the three options were complete agreement (F and R codes numerically the same, code A0), minor disagreement (F and R codes differed by 1, code A1) or maximum disagreement (F and R codes differed by 2, code A2).

An evaluation of the sensitivity of the two methods was obtained by examining whether the Frisen grading and the ranking method used by each of the six observers detected a difference between a given pair of photographs. The number of times that the Frisen grading showed a difference was compared to the number of times the rating showed a difference, for the 94 pairs of photographs.

Results were analysed for the whole cohort, as well as separately for patients with acute and chronic IIH. For the acute cohort only, the original identifications of the photographs were used to match the assigned Frisen grade and ranking with the assessment of disc status

performed as part of the IIH Trial. This allowed comparison between the blinded rating and the assessment of optic disc status at the final visit of the trial.

4.3.1.1 Statistical analysis

Statistical analyses were performed using SPSS 17.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL.) Continuous variables were analysed using descriptive statistics. Dichotomous variables were compared using the Sign test. The degree of agreement between rankings was calculated using Kendall's tau-b statistic. Significance was set at 0.05.

4.3.2 Results

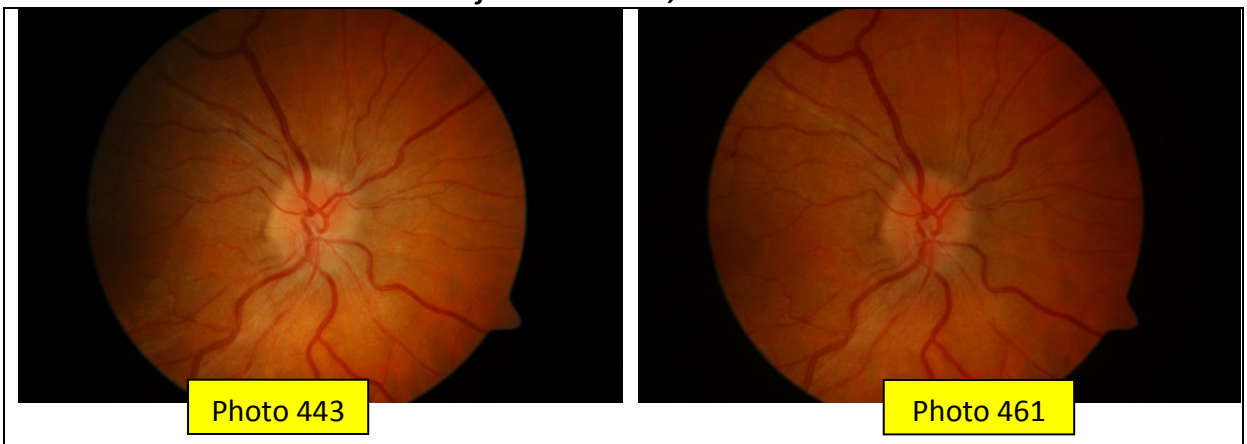
Photographs from each eye of 47 patients, before and after therapeutic intervention, were included. Thus a total of 188 photographs were assessed by each of the six observers.

Results were collated onto a single spreadsheet. A section of the spreadsheet showing results for the first ten pairs of photographs is shown in figure 4.1. Additional columns in the spreadsheet were created from the comparison of results between pairs of observers. To demonstrate how the various analyses were performed, figure 4.2 shows a worked example from the results of two observers on one pair of disc photographs.

Photo Code	Frisen Grade Assigned						Photo Code	Frisen Grade Assigned						Rank: Photo with least papilloedema or S if same					
	Ob1	Ob2	Ob3	Ob4	Ob5	Ob6		Ob1	Ob2	Ob3	Ob4	Ob5	Ob6	Ob1	Ob2	Ob3	Ob4	Ob5	Ob6
446	1	0	1	1	1	1	470	0	0	0	0	0	1	470	470	470	470	470	470
443	0	1	1	2	2	1	461	0	1	1	1	2	1	S	461	461	461	461	S
441	5	4	3	4	4	3	424	0	0	1	1	0	1	424	424	424	424	424	424
404	4	2	3	4	4	3	450	3	1	2	4	3	2	450	450	450	450	450	450
437	3	1	2	3	4	2	490	2	1	2	3	4	2	490	S	437	S	490	490
484	4	1	2	4	4	2	475	3	1	1	4	4	2	475	475	475	475	475	475
416	5	4	4	4	4	4	440	1	0	1	1	1	1	440	440	440	440	440	440
494	4	1	3	3	4	2	468	3	1	1	3	1	2	468	468	468	468	468	468
435	2	1	1	2	2	2	411	0	0	0	0	0	0	411	411	411	411	411	411
420	5	2	3	4	4	3	402	2	1	1	1	2	2	402	402	402	402	402	402

Figure 4.1: Section of results spreadsheet showing sets of results for ten pairs of photographs.

Ob1 = results from observer 1, Ob2 = observer 2 etc.



Results of Observer 1*: Frisen Grades: 443=Grade 0, 461=Grade 0. Ranked discs as same.*
Results of Observer 2*: Frisen Grades: 443=Grade 1, 461=Grade 1. Ranked photo 461 as the disc with the least papilloedema.*

Difference between assigned Frisen grade:
Photo 443: grade 0 (observer 1) compared to grade 1 (observer 2) = difference of 1 grade
Photo 461: grade 0 (observer 1) compared to grade 0 (observer 2) = difference of 1 grade

Difference between assigned Rank: Observer 1 ranked discs as same, Observer 2 selected photo 461 as showing the least papilloedema. Ranking code therefore = 1 (Minor disagreement).

Agreement between Frisen and Ranking:
Discs are considered in same chronological order, photo 443 then photo 461.
Observer 1 gave the first disc, photo 443, the same Frisen grade as the second disc, photo 461.
This result is assigned the code F1.
Observer 1 ranked the photos as the same. This result is assigned the code R1.
Observer 2 gave the first disc, photo 443, the same Frisen grade as the second disc, photo 461.
This result is assigned the code F1.
Observer 2 ranked the second disc, photo 461, as showing the least papilloedema. This is assigned the code R2.

The agreement between the Frisen and Ranking methods are as follows.
For Observer 1, F1 and R1 are numerically the same, so agreement code is A0 (Complete agreement)
For Observer 2, F1 and R2 is a difference of 1, so agreement code is A1 (Minor disagreement)

Sensitivity:
Observer 1: Frisen grade same, ranking result same. Sensitivity of two methods appears equal.
Observer 2: Frisen grade same, ranking result different. Ranking appears more sensitive.

Figure 4.2: Example of analysis applied to results for one pair of photographs by two observers

4.3.2.1 Frisen Grading

All six Frisen grades were identified, with different frequencies. The frequency of assignment of each grade is shown in figure 4.3. Grades 1 and 2 were observed most often, in both the acute and chronic cohort. Only 16 instances of Frisen grade 5 occurred (1.4%), 12 in the acute and four in the chronic patient group.

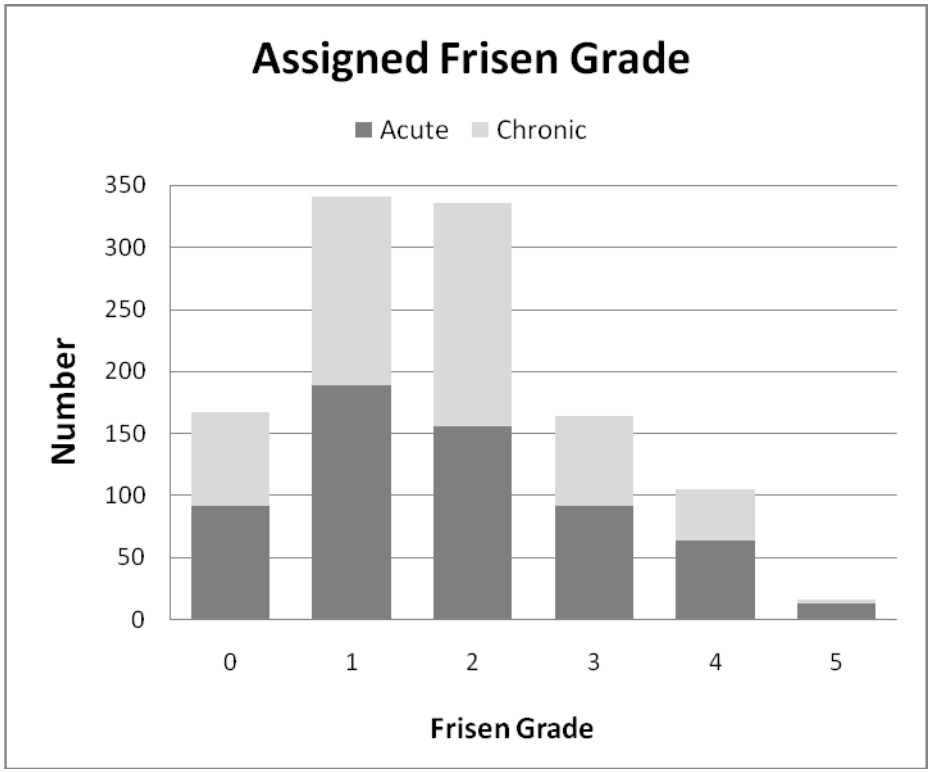


Figure 4.3: Distribution of Frisen Grades assigned by six raters by IIH cohort

There were only three instances of total agreement about the assigned Frisen grade amongst the six observers, out of a possible 188 (1.6%). In two cases, the agreed grade was 1, in one case grade 0. There were a total of 16 out of 188 instances (8.5%) in which five of the six observers agreed about the Frisen grade.

Agreement over the assigned Frisen grade between pairs of observers is shown in table 4.6. For the whole patient cohort, the number of instances where there was total agreement between pairs of raters was 1019 from a total of 2820 possible comparisons, thus the

probability of agreement was 36.1%. In contrast, there were only two instances of a difference of five Frisen grades between two raters (probability 0.1%). There was no difference between the results when acute and chronic cases were considered separately (Kendall's tau-b statistic 0.016, p=0.360).)

Table 4.6: Inter-observer variability in Frisen grading

Difference between assigned Frisen grade	*Number of instances (%)*		
	All cases	*Acute cohort*	*Chronic cohort*
0	1019 (36.1)	*545 (36.3)*	474 (35.9)
1	1288 (45.7)	696 (46.4)	592 (44.8)
2	429 (15.2)	225 (15)	204 (15.5)
3	71 (2.5)	33 (2.2)	38 (2.9)
4	11 (0.4)	1 (0.1)	10 (0.8)
5	2 (0.1)	0(0)	2 (0.2)

To examine where in the Frisen grading scale the differences were seen, the maximum assigned Frisen grades were compared with the minimum grades by cross tabulation as shown in table 4.7. For example, there were 27 occurrences of the difference being between grades 4 and 5, compared with 364 instances of the assigned grades being 0 and 1.

Table 4.7: Instances of differences between Frisen grades

		Maximum Frisen Grade					
		0	***1***	***2***	***3***	***4***	***5***
Minimum Frisen Grade	***0***	157	364	124	23	8	2
	1		373	449	104	39	3
	2			312	299	170	9
	3				107	149	31
	4					66	27
	5						4

4.3.2.2 Ranking

There were 40 instances of total agreement between the six observers when ranking the pairs of photographs according to which one had the least papilloedema, from a total of 94 comparisons (42.5%).

Agreement between pairs of observers, when all possible combinations were analysed, is shown in table 4.8. Amongst the whole cohort, the probability of agreement between raters was 71.7%. The probability of one observer judging the degree of disc swelling to be the same and one ranking the photographs as different was 24.9%.

Table 4.8: Agreement in ranking between pairs of observers

	Number of instances (%)		
Ranking code	*All*	*Acute*	*Chronic*
0 (both raters agree)	994 (71.7)	652 (87.4)	342 (52.4)
1 (minor disagreement)	349 (24.9)	85 (11.4)	264 (40.4)
2 (maximum disagreement)	56 (4.0)	9 (1.2)	47 (7.2)

There was a significant difference between the acute and chronic cases when photographs were ranked in this way. Disagreement between observers was significantly more common amongst the chronic cohort than the acute (Kendall's tau-b 0.380, $p<0.001$.)

4.3.2.3 Agreement between Frisen grading and ranking

Table 4.9 shows the results of the comparisons of Frisen grading and ranking. There were only two instances of 'maximum disagreement' (Code A2) between the two methods. One instance occurred amongst the acute cohort and one, the chronic IIH cohort. In both cases, one photograph had been assigned a higher (worse) Frisen grade, yet been ranked as the

disc with the least papilloedema. The number of instances of complete agreement between the Frisen grading and the ranking was 437 from a total of 563 (77.6%).

Table 4.9: Agreement between Frisen grade and rank

Frisen v Rank Agreement Code	*Number of Instances (%)*		
	All	*Acute*	*Chronic*
A0: Complete agreement	437 (77.6)	248 (82.7)	189 (71.9)
A1: Minor disagreement	124 (22.0)	51 (17.0)	73 (27.8)
A2: Complete disagreement	2 (0.4)	1 (0.3)	1 (0.4)

Amongst all comparisons, a difference in the ranking when there was no difference in the assigned Frisen grades occurred in 22%. When acute and chronic cases were analysed separately, the frequencies were 17% and 27.8% respectively. There was a significant difference in agreement of the Frisen grading and ranking between the acute and chronic cases. Disagreement was significantly more common amongst the chronic than the acute cohorts (Kendall's tau = 0.129, p=0.002.) On each occasion of 'minor disagreement', the difference was in the rank and not in the assigned Frisen grade.

4.3.2.4 Comparison of Sensitivities between Frisen and ranking

The comparisons between Frisen grading and ranking in the detection of a difference between pairs of photographs are summarised in table 4.10. The assigned Frisen grade was the same in 46.8% of all patients, compared with ranking which was the same in only 24.8%. Ranking of the disc (as 'same' or 'different') was significantly more likely to detect a

difference than assigning a Frisen grade (p<0.001). This was the case when acute and chronic cases were analysed separately (both p<0.001).

Table 4.10: Comparison between Frisen grading and ranking in the identification of difference between pairs of photographs by all observers

		Number (%)		
		All	***Acute***	***Chronic***
Frisen	Same	264 (46.8)	82 (27.3)	182 (68.9)
	Different	300 (53.2)	218 (72.7)	82 (31.1)
Rank	Same	140 (24.8)	31 (10.3)	108 (40.9)
	Different	424 (75.2)	269 (89.7)	156(59.1)

The assigned Frisen grades and the rank were more likely to be the same amongst the chronic than the acute cohort. The Frisen grade was different in 72.7% of acute, but only 31.1% of chronic cases. This difference was significant (Kendall's tau-b statistic =-0.565, p<0.001.) There was also a significant difference in the ranking between acute and chronic cases, where 89.7% of acute cases but only 59.1% of chronic cases were different (Kendall's tau-b statistic =-0.525, p<0.001.)

4.3.2.5 Comparison of blinded rating with IIH Trial Results

In the case of 24 pairs of photographs, data was available from the IIH Trial for comparison. The presence or absence of papilloedema was documented at each trial visit. All of the 24 patients were recorded as having papilloedema at the start of the trial. Analysis of assigned Frisen grades by all six observers to disc photographs from the start of the trial is summarised in figure 4.4. There were 15 instances (5.2%) of a Frisen grading of 0 (normal disc appearance) overall despite all patients reportedly having papilloedema.

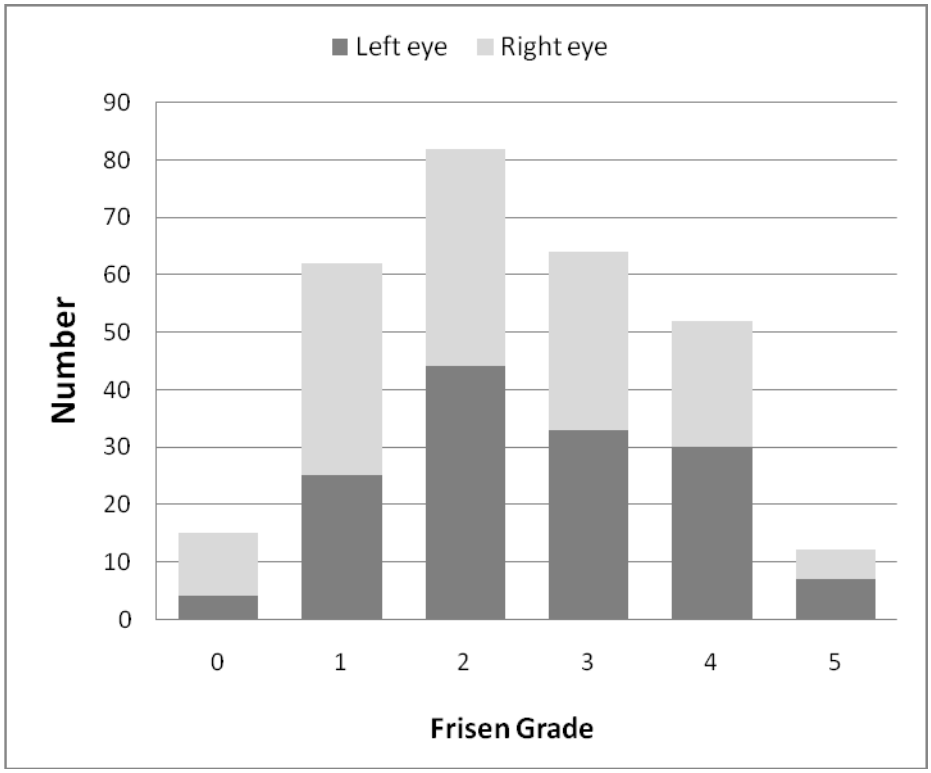


Figure 4.4: Frisen grades assigned by six blinded observers to disc photographs from 24 patients in the IIH Trial Pilot taken at the baseline trial visit

Amongst the photographs from the final visit of the trial, there were six from patients recorded as having no papilloedema and 18 from patients with papilloedema present at that visit. In the group recorded as having no papilloedema, no photographs were assigned Frisen grades of 3, 4 or 5. Equal numbers were assigned grades 0 and 1 (both 45.8%) and the remainder (8.3%) grade 2. In the group recorded as having papilloedema present, a Frisen grade of 0 was assigned in 19.9% of cases. The distribution of assigned Frisen grades is shown in figure 4.5.

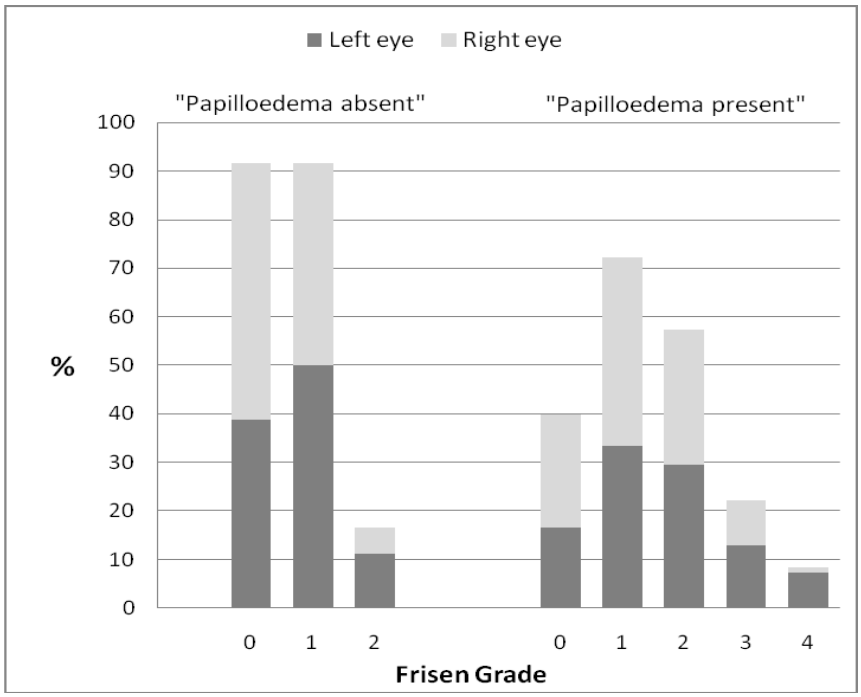


Figure 4.5: Frequencies of Frisen grades assigned by six observers to disc photographs by presence or absence of papilloedema as recorded at the IIH Trial final visit.

The Frisen grades assigned by all six raters to the photographs taken at the final visit of the IIH Trial were then compared to the assigned 'final optic disc status' as recorded at the end of the trial. Table 4.11 shows the distribution of the Frisen grades in the three categories of disc status, 'normal', 'abnormal, stable' and 'deteriorating'. No observer assigned a Frisen grade of 5 to any disc and no discs in the 'deteriorating' category had a Frisen grade of 0.

Table 4.11: Frequencies of assigned Frisen grades in blinded rater study grouped by assigned final disc status in IIH Trial Pilot

		Assigned Frisen Grade						
		0	***1***	***2***	***3***	***4***	***5***	***(Total number)***
Final Disc Status	Normal	32	43	27	6	0	0	(108)
	Abnormal, stable	44	64	35	8	5	0	(156)
	Deteriorating	0	4	6	10	4	0	(24)

The mean Frisen grade assigned by the six observers was calculated for each category of final disc status, 'normal', 'abnormal, stable' and 'deteriorating'. The mean Frisen grades in the 'normal', 'abnormal, stable' and 'deteriorating' categories were 1.1, 1.1 and 2.6, as shown in figure 4.6. When all results were analysed by category, there was no difference between the mean Frisen grades in the 'normal' and 'abnormal, stable' categories (p=0.78). The mean values in the 'deteriorating' category were significantly higher than those in categories 'normal' (p=0.002) and 'abnormal, stable' (p=0.005). Analysis of left and right eyes separately did not change the results significantly.

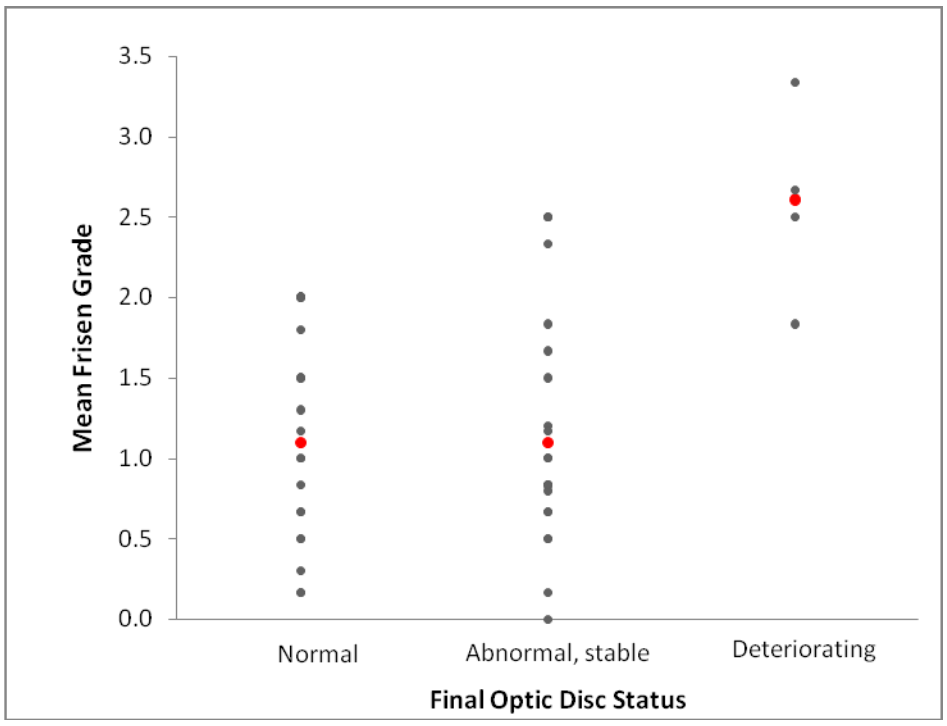
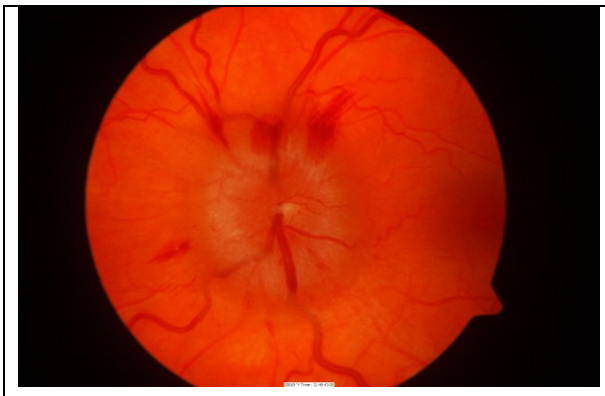


Figure 4.6: Scatter plot showing mean Frisen grades from blinded rating in the three categories of assigned optic disc status from the IIH Trial Pilot. The mean value in each group is shown in red.

The ranking of the photographs was compared to the assigned final disc status from the IIH trial. Only two of the 24 pairs of photographs were from patients whose discs were assessed in the trial as 'deteriorating' at the final visit. In one case, all six raters selected the

photograph from the baseline visit as showing the better appearance (least papilloedema), for both right and left eyes, in keeping with deterioration. All six raters also gave a higher (worse) Frisen grade to the photograph from the final visit, by at least one grade, with the exception of two instances for the right eye (16.7%). For the second patient, the results were more surprising; all six raters chose the photograph from the final visit as showing the better appearance (both eyes) and most of the assigned Frisen grades showed improvement (in the right eye, five improved and one was unchanged, in the left eye also five improved and one was unchanged). Thus the blinded rating suggested improvement over the 12-month period despite the assessment of the disc in the IIH Trial as 'deteriorating'. The disc photographs with their assigned Frisen grading are shown in figure 4.7.

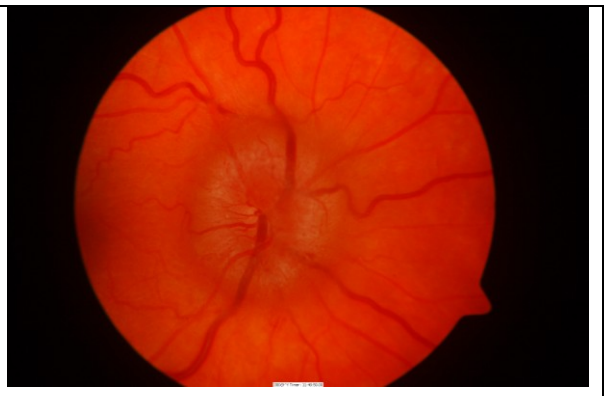
To explore this finding, data from the IIH trial for the patient in question was examined. The Humphrey visual field MD values at baseline were -7.39 (left) and -4.12 (right). At the final visit the values had improved, to -4.39 (left) and -2.15 (right). Visual acuity was unchanged between visits. The headache score had worsened, from 6 at baseline to 9 at the final visit and tinnitus as well as headache status were described as 'deteriorating' at the final visit, when the overall IIH status was also recorded as 'active IIH deteriorating'.



Baseline visit, left eye:

Assigned Frisen grades 2,3,3,4,4 and 4

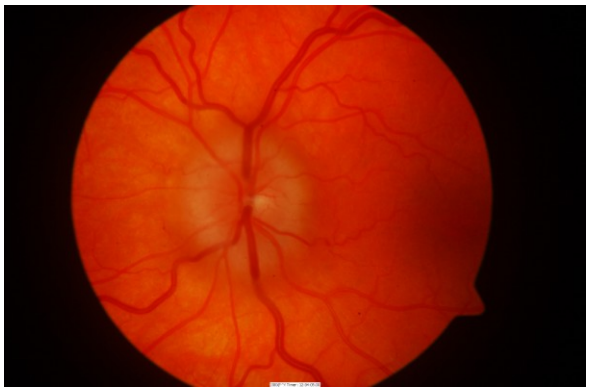
mean = 3.3



Baseline visit, right eye:

Assigned Frisen grades 1,2,3,3,4 and 4

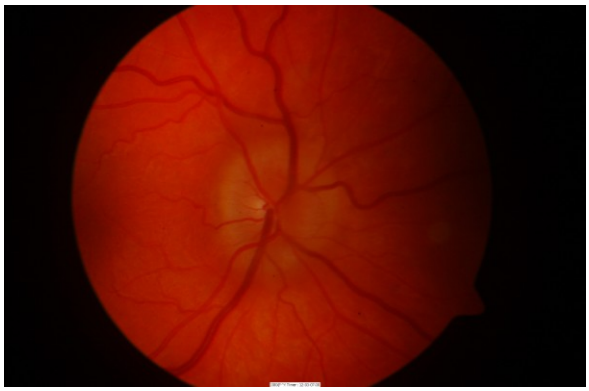
mean = 2.8



Final visit, left eye:

Assigned Frisen grades 1,2,2,3,3 and 4,

mean = 2.5



Final visit, right eye:

Assigned Frisen grades 1,1,1,2,3 and 3

mean = 1.8

Figure 4.7: Optic disc photographs from one patient in the IIH Trial Pilot as included in the blinded rater study, showing the assigned Frisen grades by the six observers

4.3.3 Discussion

4.3.3.1 Inter-rater variability

In this study, complete agreement between six observers over the assigned Frisen grades of 188 photographs occurred in just 1.6%. The probability of two raters agreeing completely, a measure of the inter-rater reliability, was only 36.1%. Any two raters were more likely to disagree by one grade (probability 45.7%). There was thus high variability between the observers, with probability of disagreement by at least one Frisen grade of 63.9%.

The greatest variability occurred amongst the lowest Frisen grades (0-2). Interestingly, the inter-observer reliability of Frisen grading was equivalent when cases were separated into acute and chronic cohorts (probabilities of same grade assigned 36.3% and 35.9% respectively, p=0.360). This is reflected in the spread of Frisen grades within the two cohorts (Figure 1).

In the original paper by Frisen, (1982) three observers reached exact agreement about the Frisen grade in 49% of 78 photographic slides. In the study by Karam and Hedges, (2005) two observers reached agreement over the grade in 62% of 104 photographs. The patient groups in both studies were heterogeneous. No study has evaluated the Frisen staging scheme in IIH.

The method of ranking the discs showed greater agreement between observers. Complete agreement was seen in 42.5% and inter-rater reliability was 71.7%. The effect of the number of options within each system (six possible Frisen grades but only three choices for ranking) is likely to contribute to this finding, although it is difficult to quantify.

4.3.3.2 Sensitivity

Ranking disc photographs according to the severity of papilloedema appears to be more sensitive than relying on Frisen grades to detect a difference. The ranking method identified a difference in 75.2% of photographs compared to 53.2% detected by the Frisen grading, an increase of 22%. This difference was even more pronounced amongst the chronic IIH cohort (27.8% compared to 17.0% difference in acute cases.) When Frisen grading and ranking were compared, 'minor disagreement' (Code A1) always described a situation in which the Frisen grade remained the same, but a difference was observed in the ranking, (22.0% of cases). The situation of a pair of photographs being assigned different Frisen grades yet not ranked in severity did not occur. The two instances of 'maximum disagreement' (Code A2) between the Frisen grading and the ranking (one photograph assigned a higher Frisen grade, yet ranked as the disc with least papilloedema) are likely to represent observer error.

The assessment of papilloedema in IIH appears to be affected by the duration of the disease. There was a significant difference in the sensitivity of both methods of assessing disc appearance between acute and chronic IIH cases, such that both Frisen grading and ranking had greater sensitivity amongst the acute cohort (both $p<0.001$). This contrasts with the inter-observer variability of the two methods, which was affected differently by the disease chronicity. Whilst there was no difference in the inter-observer variability of Frisen grading between the acute and chronic cases ($p=0.360$), there was a greater degree of variability amongst the chronic cases than the acute cohort when ranking the photographs. The probability of any two observers agreeing was 87.4% in the acute cases, but only 52.4% in the chronic IIH cases and the difference was significant ($p<0.001$).

4.3.3.3 IIH Trial Data Comparisons

Comparison between the Frisen grading system and the assessment of papilloedema in the IIH Trial revealed marked inconsistencies. A Frisen grade of 0, describing normal optic discs, was assigned to discs recorded as having papilloedema in 5.2% of instances at the initial trial visit and 19.9% of instances at the final (12-month) visit. Similarly, amongst patients recorded as having no papilloedema at the final visit, grades other than 0 were assigned in over half of instances (54.1%).

In addition, when the subjective assessments of optic discs in the IIH Trial Pilot were compared with the results of the blinded rating, only 29.6% of discs assigned a final status of 'normal' had a Frisen grade of 0. The assigned Frisen grade did not discriminate between discs in the categories of 'normal' and 'abnormal, stable'. Discs assessed as 'deteriorating' in the trial did have a significantly higher mean Frisen grade, although numbers were too small to draw meaningful conclusions (n=4).

Possible explanations exist for these findings. First, the IIH Trial considered disc status as applicable to both eyes, where the blinded rating assessed left and right eyes separately. In the IIH Trial, 'papilloedema present' could refer to a case of asymmetrical or unilateral papilloedema, such that Frisen grade for each eye could vary considerably and include grade 0 for one eye. The assigned status of 'normal' optic disc status in the IIH trial could be applied to eyes which had no signs of active papilloedema, but whose photographs showed some degree of abnormality such that a Frisen grade of 0 was not appropriate. Longstanding papilloedema results in changes to the optic disc that are not fully reversible.(Acheson, 2006) Markers of chronicity include disc pallor, choroido-retinal collateral blood vessels and axonal degradation products on the optic nerve head (corpora amylacea). (Sanders, 1997)

Such changes are not accommodated within the Frisen staging scheme, designed to describe disc swelling during its development. Clinical experience suggests that a majority of patients with longstanding IIH have optic disc appearances that never return to a truly 'normal' state as described by Frisen grade 0.

Further comparison between the assessment of papilloedema in the IIH Trial and that of the blinded rating study data is limited by the marked differences in the methods. The IIH trial required a subjective assessment at the final trial visit, based on the three-dimensional appearance of the optic discs on slit lamp examination. The assessing clinician had access to clinical information to inform his or her judgment, including other tests of visual function that would bias the conclusion reached. In contrast, the blinded rating study involved assessment of a single, two-dimensional disc photograph with no clinical information provided.

There are other limitations to this study. Stereoscopic retinal photography was not available and the images obtained were two-dimensional, although this was also the case in the original description and validation of the Frisen scheme. In normal practice, the assessing clinician uses a slit lamp to obtain a highly magnified, three-dimensional view of the retina, allowing additional features not captured by the Frisen scheme to be appreciated. The need for blinding or masking of clinical information precludes the use of slit lamp examination in most clinical trials so a comprehensive descriptor of the features and severity of papilloedema in IIH is required.

The observers performed the assessment of the discs on a single occasion in this study, so no measure of intra-rater reliability could be made. This was for practical considerations due to the time-consuming nature of the assessments (188 photographs for each observer to

examine, grade and compare in pairs). Fatigue amongst observers could have led to an error rate which is difficult to quantify. It is also impossible to draw firm conclusions from this study about the optimum number of observers to recommend for future similar studies.

4.3.3.4 Recommendations

Given the limitations of the Frisen scheme, there is a need for a novel classification of papilloedema that would encompass most of the changes seen in IIH, including those that occur in chronic forms of the disease. In order for such a scheme to be included in pragmatic trials, it would need to have high reliability and sensitivity as well as reproducibility. Any alternative grading scheme proposed for the evaluation of papilloedema in IIH would require rigorous testing to address this.

Each grade would require a clear illustration of the key features. Categories of the classification would need to reflect the subtle changes seen in longstanding IIH and allow for additional features such as haemorrhages to be commented upon. Johnson et al(Johnson et al., 1998) used photographic 'gold standards' for their assessment of papilloedema in the study exploring weight loss and acetazolamide treatment in IIH. However, the disc photographs they used were not exclusively from patients with IIH and they adopted a four-grade system based on the Frisen scheme, with no allowance for the changes of longstanding disc swelling or clinical improvement. It is feasible that future studies could explore the development of an agreed set of standard photographic examples of papilloedema in IIH, including examples of discs exhibiting the residual changes of treated disease.

More objective assessments of papilloedema such as optical coherence tomography (OCT) and confocal scanning laser ophthalmoscopy (SLO) should be further explored in IIH. Case reports and small studies have shown that OCT demonstrates measurable differences in the retinal nerve fibre layer that can relate to papilloedema severity as measured clinically. (Hudson et al., 1995; Karam and Hedges, 2005) Mulholland et al (1998) carried out a study in which confocal SLO was used to assess papilloedema in eight patients with IIH. Cases of acute, chronic and recurrent disease were included and the sensitivity of the method was clearly demonstrated. The volumes of optic disc swelling were significantly different between the left and right eyes despite the Frisen grading showing no difference, in all cases. SLO was also shown to correlate closely with changes in Humphrey visual field mean deviation in the early stages of acute disease and to demonstrate the effect of treatment by detecting stable, decreasing or increasing disc volume. However, the degree of disc swelling was not related to the visual function in established disease. Decreasing volume may indicate resolution of papilloedema, but is also seen in secondary optic atrophy, so other measures of visual function remain important. Despite the accuracy of measures of optic disc volume such as SLO and OCT, they cannot be relied upon to fully evaluate papilloedema in IIH. In addition, the availability of the techniques is currently restricted to specialist centres. Nevertheless, such techniques may have important roles in future clinical trials.

This study provides evidence that the Frisen staging scheme is insufficiently sensitive, specific and reliable to justify its use as a major outcome measure in trials of IIH. Alternative grading schemes should be sought and evaluated. Until such alternatives are defined, comparison or ranking of discs according to the degree and severity of papilloedema appears to be a better tool in the evaluation of IIH. Whilst such an approach is simplistic and

subjective, its demonstrated greater sensitivity to change and inter-rater reliability has much to recommend it as an alternative to the Frisen scheme.

CHAPTER 5 CONCLUSIONS

Since its original description over 100 years ago, uncertainty has surrounded the condition of idiopathic intracranial hypertension. Even the diagnostic criteria are contentious: whilst many clinicians and researchers adhere to the modern 'strict' criteria of raised intracranial pressure for which no cause can be identified, in keeping with the term idiopathic, there are supporters of a broader terminology, in which the diagnosis of pseudotumour syndrome allows for the inclusion of conditions where some identified factor, such as venous sinus thrombosis or medication, is the cause of the raised pressure. There is convincing evidence that truly idiopathic IIH is a discrete clinical entity, affecting overweight, young to middle age females in the great majority of cases. Why IIH occurs at all amongst less typical groups, such as males and young children, remains unclear, but these patients in particular warrant exhaustive investigation to exclude an alternative cause of their elevated pressure. The exclusion of occult cerebral venous sinus thrombosis by the most sensitive imaging modality available is mandatory in all cases. Screening for anaemia is recommended due to its common occurrence and the clinical improvement that results from its correction. (Mollan et al., 2009)

5.1 Obesity and IIH Pathogenesis

The high prevalence of obesity in IIH has greatly influenced the direction of attempts to discover its cause as well as to determine successful management strategies. The association of IIH with female gender and obesity is robust and widely accepted. Using this association as the basis for aetiological studies has yielded promising results, despite failing to explain

the occurrence of the condition in other patient groups. The finding of elevated leptin in the CSF of a cohort of female patients, described in chapter 2, provides a promising link between the inflammatory state of obesity and IIH. The fact that the actions of leptin are influenced by gender adds strength to the theory that this adipokine has a role in IIH pathogenesis. The case for dysregulation of leptin at the level of the hypothalamic receptors playing a key role is supported. An alternative hypothesis, that leptin dysregulation in IIH actually causes or potentiates the obesity in IIH is worthy of consideration.

The finding of significantly elevated CSF leptin as well as its non-linear relationship with BMI and CSF pressure amongst patients with IIH should firstly be confirmed in larger cohorts of human subjects, although such studies are restricted by the ethics of obtaining CSF samples from healthy overweight controls. Exploration of leptin action at the cellular level, in structures likely to be related to IIH pathogenesis, would be of value. Reduced absorption of the CSF appears to be the most plausible of the mechanisms to explain the elevated pressure, but most data so far has been from animal studies. The actions of peptide molecules and their receptors at the arachnoid granulations are largely unknown. Studies using human tissue from post mortem examinations are needed to determine whether impairment of arachnoid function or metabolic failure of transport across the arachnoid-endothelial barrier underlies the disease process in IIH. Arachnoid granulations would seem an appropriate initial target for histochemical studies, which should include investigation of the actions of leptin.

5.2 Management of IIH

The optimum management of IIH is almost as widely debated as its underlying cause. Consensus has been reached over the need for careful monitoring of visual function in light of the established occurrence of blindness in the condition, albeit infrequently. The use of perimetry in identifying visual dysfunction has also been widely adopted in routine clinical practice. How to identify patients at greatest risk of visual loss and how best to treat them remains undetermined and the need for evidence from well designed clinical trials is universally acknowledged.

The IIH Trial Pilot, reported in chapter 3, highlights the practical difficulties of conducting randomised, controlled trials in the condition. IIH is not uncommon and the rising prevalence of obesity suggests the incidence will increase. Nevertheless, recruitment of 50 patients from five centres in this trial took almost two years. A sample size of around 300 patients would be required for a substantive trial using similar outcome measures, so extended recruitment periods or expansion to multiple centres would need to be undertaken. No patient in the pilot became blind and only two of the 50 patients required surgical intervention. To detect treatment effects upon meaningful outcomes, such as blindness, significant visual loss or need for surgery, would require even greater numbers of subjects.

The patients recruited in this pilot under-represent those with the greatest threat of blindness and instead tended to include patients with a mild, self- limiting course irrespective of intervention. One concern with the findings of this trial would be the implication that IIH is always a benign condition, thus relaxing the approach of clinicians in monitoring vision. In fact, the lack of clear markers of impending visual damage in IIH demands even greater vigilance amongst neuro-ophthalmologists, since patients lose vision

unpredictably and often when exhibiting very few symptoms or signs. Future IIH trials must strive to focus on the management of more aggressive disease. The concept of randomised controlled trials comparing optic nerve sheath fenestration with CSF diversion procedures, or comparing ventriculoperitoneal with lumboperitoneal shunts are enticing, but practical difficulties of low patient numbers and local preferences for certain procedures limit the likelihood of such trials going ahead. Patients would be unlikely to consent to join trials in which the choice between two such different procedures was left to chance. Pragmatic solutions must be found to ensure that trials are large enough for robust conclusions to be drawn, yet capture patients with more severe disease, whose course is most likely to be influenced by treatment.

The prescription of acetazolamide in IIH should be questioned. There have been no prospective, randomised controlled trials to justify its widespread use. Whilst not powered to show a treatment effect, the IIH Trial Pilot showed that the drug was poorly tolerated or that patients were disinclined to take it. Again, the bias towards milder disease limits the wider applicability of this observation and the lack of use of placebo in the trial can be criticised. There was a trend towards greater weight reduction amongst the patients allocated to receive acetazolamide and it is known to affect taste. It is feasible that some of its apparent effect in IIH is exerted via appetite suppression or dietary modification resulting in weight loss.

Although the final outcome was not observed to be influenced by weight loss in this pilot study, there is growing evidence in the literature to suggest that weight reduction is a key component of IIH management. (Johnson et al., 1997; Sinclair et al., 2009) Future trials amongst patients with milder or chronic forms of IIH would seem to be more appropriately

focussed on careful assessment of the effect of weight reduction than that of acetazolamide or other diuretics. It would be unethical to design trials in which patients were encouraged not to lose weight, but patients could be randomly allocated to receive either a supervised, intensive low calorie diet such as that used by Sinclair et al (2009) or the standard dietary advice provided in current NHS practice. Comparison could then be made between 'intensive' weight management strategies and routine dietary advice, as well as acetazolamide treatment with and without weight reduction, using a 2x2 factorial design.

5.3 Outcome Measurement

Whilst a single outcome measure for IIH has not been identified, this and other studies have demonstrated that often a combination of symptoms and examination findings in IIH determine the action taken by treating clinicians. A simple scoring system has been tested, based on the most common clinical symptoms and signs (headache, tinnitus, visual obscurations, acuity, visual field and papilloedema) and its use demonstrated in the 50 patients. Visual field assessment and optic disc appearance have been shown to exert the greatest influence on clinical decision-making, but other features of the assessment are also taken into account. This was reflected in the relative concordance of the various components of the score upon the final outcome and further corroboration of the findings is warranted. There is great potential for the creation of a composite outcome measure for patients with IIH using these key clinical features that can be easily reproduced and modified for lager studies. The use of blinding would improve the tool and compensate for its subjective nature, but would involve additional personnel. The desire to reduce bias through blinding must always be carefully balanced against the strength of the pragmatic trial design

in evaluating normal clinical practice. A composite score should be tested at all time points in subsequent trials, and not restricted to the final visit as in this study. In addition, weighting could be added to reflect the importance of visual field and optic disc assessments in the overall evaluation and is worthy of further study, along with rigorous evaluation of the reliability and validity of the tool.

Visual fields remain the 'gold standard' for measurement of visual function in IIH, despite the recognised limitations of functional variations and learning effect. (Keltner, 2000) Even when modern techniques such as optical coherence tomography and scanning laser ophthalmoscopy are used to accurately measure the papilloedema they fail to show differences that significantly correlate with visual dysfunction (Mulholland et al., 1998). The place of perimetry in the clinical evaluation of IIH is assured until newer technologies of equivalent sensitivity and improved reliability emerge.

5.4 Assessment of Papilloedema in IIH

Optic disc appearance also remains a critical indicator of the clinical status in IIH. Various factors influence the appearance of the optic disc, such as intracranial pressure fluctuations, duration of elevated pressure and morphology, perfusion and susceptibility of the disc itself, as discussed in chapter 1. Attempts to classify the optic disc in IIH must take account of these factors as well as the effect of duration on the appearance of papilloedema. The commonly used Frisen staging scheme fails to reflect resolving papilloedema and optic atrophy, as well as failing to describe the subtle changes noted on clinical examination of the patient with IIH. In the assessment of papilloedema in patients with IIH of recent onset as well as more longstanding disease, the Frisen scheme has been shown to have poor

sensitivity and reliability, as reported in chapter 4. Ranking papilloedema severity has been shown by the study to exhibit superior inter-observer reliability and sensitivity to change, especially in cases of chronic disease.

Use of the Frisen grading scheme in IIH needs to be replaced with a novel, validated and more clinically applicable system. This would need to identify and describe features of evolving, stable and improving papilloedema, rather than give a rigid classification. Until such a scheme exists, it would appear there is a role for simple ranking of discs by masked observers as a pragmatic solution for the much-needed large trials in IIH.

5.5 Conclusions and Recommendations

In conclusion, this thesis has addressed key areas in the study of IIH. (Table 5.1) A role for leptin in the relationship between IIH and both obesity and female gender is strongly suggested by the novel finding of elevated CSF leptin. Future goals for pragmatic trials have been identified, to evaluate the effect of treatment, especially weight reduction. The innovative use of a composite outcome measure has been tested and a scoring system proposed as a useful tool in IIH assessment. Finally, the need to replace the use of the Frisen scheme in the assessment of papilloedema in IIH has been clearly demonstrated.

Recommendations for future work leading on from the findings of this thesis are also summarised in table 5.1. Assays of leptin should be repeated amongst larger IIH cohorts and matched controls, under stricter metabolic conditions as well as repeated at various time points throughout the course of the disease. Examination of the actions of leptin at a cellular level should target the arachnoid granulations to explore its effect, if any, on CSF outflow.

Table 5.1: Summary of Key Findings and Recommendations

Theme	Findings	Recommendations
IIH Pathophysiology	Significant elevation of CSF leptin levels in patients with IIH compared to matched controls Cytokines identified in IIH but not in a classically inflammatory profile	Corroborate findings with larger, controlled studies of leptin in IIH Cellular and histochemical studies focussing on arachnoid granulations and CSF absorption pathways
Trial Design	50 patients prospectively recruited to randomised controlled trial pilot	Substantive trial to recruit minimum of 300 subjects Retain pragmatic design for future trials
Trial subjects	Low incidence of visual dysfunction and need for surgery in population studied Poor compliance with acetazolamide	Early recruitment and other measures to include patients at greater risk of visual loss in future trials Include intensive weight loss arm in future randomised trials
Outcome measures	Visual fields and optic disc appearance best indicators of disease status Main clinical features of IIH create an effective composite scoring system	Weighting of composite scoring systems to reflect importance of perimetry and optic disc appearance Formal study of the validity and reliability of composite scoring systems in IIH
Assessment of papilloedema in IIH	Frisen staging scheme has low inter-rater reliability and sensitivity in IIH Ranking discs has greater reliability and sensitivity	Novel papilloedema classification for IIH to replace Frisen scheme Blinded disc ranking as alternative to Frisen in pragmatic trials Evaluation of objective techniques of papilloedema measurement in IIH

A multi-centre clinical trial should be undertaken, to prospectively assess a minimum of 300 patients with newly diagnosed IIH, with treatment arms including intensive dietary intervention, intensive dietary intervention plus acetazolamide, acetazolamide alone and no intervention, except for the standard advice to lose weight, which should be given to all overweight subjects. A pragmatic trial design should be adopted to ensure adequate recruitment. Outcome measurement should include the use throughout of a scoring system comprising the key clinical features, weighted to attach greatest importance to optic disc swelling and visual field abnormalities. The validity and reliability of such a scale could be confirmed by studies in clinical settings prior to its use in a substantive trial. The creation of a bespoke grading scheme for the accurate assessment of papilloedema in IIH, to replace the Frisen scheme, should also be a priority and its validation could include comparisons with objective measurement by optical coherence tomography.

Whilst IIH is not a common disorder, it is likely to become more so as the population gains weight. For many sufferers, it is a long term condition with high levels of morbidity and disability. For some, it is a sight threatening condition. For these reasons, IIH must remain a focus for careful further study. The findings in this thesis provide valuable insight into the directions that such research should follow.

LIST OF REFERENCES

Acaroglu, G., Y. Özdamar, et al. (2002). "Pseudopapilloedema and headache: pseudo-pseudotumour cerebri?" Neuro-Ophthalmology **28**(1): 13-21.

Acheson, J. F. (2004). "Optic nerve disorders: role of canal and nerve sheath decompression surgery." Eye **18**(11): 1169-74.

Acheson, J. F. (2006). "Idiopathic intracranial hypertension and visual function." Br Med Bull **79-80**: 233-44.

Ahima, R. S. (2004). "Body fat, Leptin and Hypothalamic amenorrhoea." New England Journal of Medicine **351**(10): 959-962.

Aleffi, S., I. Petrai, et al. (2005). "Upregulation of proinflammatory and proangiogenic cytokines by leptin in human hepatic stellate cells." Hepatology **42**(6): 1339-48.

Amaral, J., W. Tsiaris, et al. (1987). "Reversal of Benign Intracranial Hypertension by Surgically Induced Weight Loss." Archives of Surgery **122**: 946-949.

Antaraki, A., G. Piadites, et al. (1993). "Octreotide in benign intracranial hypertension [letter]." Lancet **342**(8880): 1170.

Backhouse, O., T. Metcalfe, et al. (1998). "Factor V Leiden mutation in association with idiopathic intracranial hypertension." British Journal of Ophthalmology **82**(7): 844.

Backhouse, O. C. (2001). "Idiopathic intracranial hypertension and anticardolipin antibodies." Journal of Neurology, Neurosurgery & Psychiatry **70**(3): 420-1.

Bado, A., S. Levasseur, et al. (1998). "The stomach is a source of leptin." Nature **394**(6695): 790-3.

Bailey, I. L. and J. E. Lovie (1976). "New design principles for visual acuity letter charts." Am J Optom Physiol Opt **53**(11): 740-5.

Bailey, I. L. and J. E. Lovie (1980). "The design and use of a new near-vision chart." Am J Optom Physiol Opt **57**(6): 378-87.

Bakshi, S. K., J. L. Oak, et al. (1992). "Facial nerve involvement in pseudotumor cerebri." J Postgrad Med **38**(3): 144-5.

Banta, J. T. and B. K. Farris (2000). "Pseudotumor cerebri and optic nerve sheath decompression." Ophthalmology **107**(10): 1907-12.

Bastin, M. E., S. Sinha, et al. (2003). "Diffuse brain oedema in idiopathic intracranial hypertension: a quantitative magnetic resonance imaging study." Journal of Neurology, Neurosurgery & Psychiatry **74**(12): 1693-6.

Bell, L. N., J. L. Ward, et al. (2006). "Adipose tissue production of hepatocyte growth factor contributes to elevated serum HGF in obesity." Am J Physiol Endocrinol Metab **291**(4): E843-8.

Berg, A. H., T. P. Combs, et al. (2002). "ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism." Trends Endocrinol Metab **13**(2): 84-9.

Berg, A. H. and P. E. Scherer (2005). "Adipose tissue, inflammation, and cardiovascular disease." Circ Res **96**(9): 939-49.

Berman, E. L. and J. D. Wirtschafter (1992). "Improvement of optic nerve head appearance after surgery for pseudotumor cerebri." Jama **267**(8): 1130.

Bicakci, K., S. Bicakci, et al. (2006). "Perfusion and diffusion magnetic resonance imaging in idiopathic intracranial hypertension." Acta Neurol Scand **114**(3): 193-7.

Binder, D. K., J. C. Horton, et al. (2004). "Idiopathic intracranial hypertension." Neurosurgery **54**(3): 538-51.

Biousse, V., A. Ameri, et al. (1999). "Isolated intracranial hypertension as the only sign of cerebral venous thrombosis." Neurology **53**(7): 1537-42.

Biousse, V., J. C. Rucker, et al. (2003). "Anemia and papilledema." American Journal of Ophthalmology. **135**: 437-446.

Boddie, H. G., M. Banna, et al. (1974). ""Benign" intracranial hypertension. A survey of the clinical and radiological features, and long-term prognosis." Brain **97**(2): 313-26.

Bono, F., M. R. Lupo, et al. (2002). "Obesity does not induce abnormal CSF pressure in subjects with normal cerebral MR venography." Neurology **59**: 1641-1643.

Bono, F. and A. Quattrone (2009). "Idiopathic intracranial hypertension without papilloedema in headache sufferers." Cephalalgia.

Bornstein, S. R., K. Uhlmann, et al. (1997). "Evidence for a novel peripheral action of Leptin as a metabolic signal to the adrenal gland. Leptin inhibits cortisol release directly." Diabetes **46**: 1235-1238.

Boulton, M., A. Young, et al. (1996). "Drainage of CSF through lymphatic pathways and arachnoid villi in sheep: measurement of 125I-albumin clearance." Neuropathol Appl Neurobiol **22**(4): 325-33.

Brodsky, M. C. and M. Vaphiades (1998). "Magnetic resonance imaging in pseudotumor cerebri." Ophthalmology **105**(9): 1686-93.

Brooks, R., R. Rabin, et al. (2003). The Measurement and Valuation of Health Status Using EQ-5D: A European Perspective

Kluwer Academic Publishers.

Bruce, B. B., S. Kedar, et al. (2009). "Idiopathic intracranial hypertension in men." Neurology **72**(4): 304-9.

Bruce, B. B., P. Preechawat, et al. (2008). "Racial differences in idiopathic intracranial hypertension." Neurology **70**(11): 861-7.

Bulens, C., J. D. Meerwaldt, et al. (1988). "Spatial contrast sensitivity in benign intracranial hypertension." Journal of Neurology, Neurosurgery & Psychiatry **51**(10): 1323-9.

Bynke, G., G. Zemack, et al. (2004). "Ventriculoperitoneal shunting for idiopathic intracranial hypertension." Neurology. **63**: 1314-1316.

Cannella, B. and C. S. Raine (1995). "The adhesion molecule and cytokine profile of multiple sclerosis lesions." Annals of Neurology **37**(4): 424-435.

Capobianco, D. J., P. W. Brazis, et al. (1997). "Idiopathic Intracranial Hypertension and Seventh Nerve Palsy." Headache: The Journal of Head and Face Pain **37**(5): 286-288.

Caro, J., J. Kolaczynski, et al. (1996). "Increased cerebrospinal fluid / serum leptin ratio in obesity: a possible mechanism for leptin resistance." The Lancet **348**: 159-61.

Casabiell, X., V. Pineiro, et al. (1998). "Gender differences in both sponteneous and stimulated leptin secretion by human omental adiopose tissue in vitro: Dexamethasone and Estradiol stimulate leptin release in women, but not in men." Journal of Clinical Endocrinology & Metabolism **83**: 2149-2155.

Casabiell, X., V. Pineiro, et al. (2001). "Leptin, Reproduction and Sex Steroids." Pituitary **4**(1-2): 93.

Castellarin, A. A., I. K. Sugino, et al. (1997). "Clinicopathological correlation of an excised choroidal neovascular membrane in pseudotumour cerebri." Br J Ophthalmol **81**(11): 994-1000.

Celebisoy, N., F. Gokcay, et al. (2007). "Treatment of idiopathic intracranial hypertension: topiramate vs acetazolamide, an open-label study." Acta Neurol Scand **116**(5): 322-7.

Chandra, V., S. N. Bellur, et al. (1986). "Low CSF protein concentration in idiopathic pseudotumor cerebri." Ann Neurol **19**(1): 80-2.

Chandrasekaran, S., P. McCluskey, et al. (2006). "Visual outcomes for optic nerve sheath fenestration in pseudotumour cerebri and related conditions." Clin Experiment Ophthalmol **34**(7): 661-5.

Chiu, A. M., W. L. Chuenkongkaew, et al. (1998). "Minocycline treatment and pseudotumor cerebri syndrome." American Journal of Ophthalmology **126**(1): 116-21.

Cinciripini, G. S., S. Donahue, et al. (1999). "Idiopathic intracranial hypertension in prepubertal pediatric patients: characteristics, treatment, and outcome." American Journal of Ophthalmology **127**(2): 178-82.

Condon, B., J. Patterson, et al. (1986). "Use of magnetic resonance imaging to measure intracranial cerebrospinal fluid volume." Lancet **1**(8494): 1355-7.

Considine, R., M. Sinha, et al. (1996). "Serum immunoreactive -leptin concentrations in normal-weight and obese humans." New England Journal of Medicine **334**: 292-5.

Corbett, J. and M. P. Mehta (1983). "Cerebrospinal fluid pressure in normal obese subjects and patients with pseudotumour cerebri." Neurology (Cleveland) **33**: 1386-8.

Corbett, J., P. Savino, et al. (1982). "Visual loss in pseudotumour cerebri." Archives of Neurology **39**: 461-474.

Corbett, J. J. (2008). "The first Jacobson Lecture. Familial idiopathic intracranial hypertension." J Neuroophthalmol **28**(4): 337-47.

Corbett, J. J. and H. S. Thompson (1989). "The rational management of idiopathic intracranial hypertension." Archives of Neurology **46**(10): 1049-51.

Cote, M., P. Mauriege, et al. (2005). "Adiponectinemia in visceral obesity: impact on glucose tolerance and plasma lipoprotein and lipid levels in men." J Clin Endocrinol Metab **90**(3): 1434-9.

Craig, J. J., D. A. Mulholland, et al. (2001). "Idiopathic intracranial hypertension; incidence, presenting features and outcome in Northern Ireland (1991-1995)." Ulster Medical Journal **70**(1): 31-5.

Curnow, S. J., F. Falciani, et al. (2005). "Multiplex bead immunoassay analysis of aqueous humor reveals distinct cytokine profiles in uveitis." Invest Ophthalmol Vis Sci **46**(11): 4251-9.

Czosnyka, M. and J. D. Pickard (2004). "Monitoring and interpretation of intracranial pressure." J Neurol Neurosurg Psychiatry **75**(6): 813-21.

Dagogo-Jack, S., G. Selke, et al. (1997). "Robust leptin secretory responses to dexamethasone in obese subjects." Journal of Clinical Endocrinology & Metabolism **82**: 3230-3233.

Dandona, P., R. Weinstock, et al. (1998). "Tumor necrosis factor-alpha in sera of obese patients: fall with weight loss." Journal of Clinical Endocrinology & Metabolism **83**(8): 2907-10.

Dandy, W. E. (1937). "Intracranial pressure without brain tumour. Diagnosis and treatment." Annals of Surgery **106**: 492-513.

Daniels, A. B., G. T. Liu, et al. (2007). "Profiles of obesity, weight gain, and quality of life in idiopathic intracranial hypertension (pseudotumor cerebri)." Am J Ophthalmol **143**(4): 635-41.

Davidoff, L. M. (1956). "Pseudotumor cerebri; benign intracranial hypertension." Neurology **6**(9): 605-15.

De Pergola, G. and N. Pannacciulli (2002). "Coagulation and fibrinolysis abnormalities in obesity." J Endocrinol Invest **25**: 899-904.

Digre, K. and J. Corbett (1988). "Pseudotumour Cerebri in men." Archives of Neurology **45**: 866-872.

Digre, K., M. Varner, et al. (1984). "Pseudotumour cerebri and pregnancy." Neurology **34**: 721-9.

Digre, K. B., B. K. Nakamoto, et al. (2009). "A comparison of idiopathic intracranial hypertension with and without papilledema." Headache **49**(2): 185-93.

Dogulu, C. F., E. Tsilou, et al. (2004). "Idiopathic intracranial hypertension in cystinosis." Journal of Pediatrics **145**(5): 673-8.

Dolan, P., C. Gudex, et al. (1995). A Social Tariff for EuroQol: Results from a UK General Population Survey. York, Publications Unit, Centre for Health Economics, University of York.

Donahue, S. P. (2000). "Recurrence of idiopathic intracranial hypertension after weight loss: the carrot craver." American Journal of Ophthalmology **130**(6): 850-1.

Donaldson, J. (1981). "Pathogenesis of pseudotumour cerebri syndromes." Neurology **31**: 877-880.

Donaldson, J. and M. Binstock (1981). "Pseudotumour cerebri in an obese woman with Turner syndrome." Neurology **31**: 758-760.

Donaldson, J. and E. Horak (1982). "Cerebrospinal fluid oestrone in pseudotumour cerebri." Journal of Neurology, Neurosurgery & Psychiatry **45**: 743-746.

Donnet, A., P. Metellus, et al. (2008). "Endovascular treatment of idiopathic intracranial hypertension: clinical and radiologic outcome of 10 consecutive patients." Neurology **70**(8): 641-7.

Duggal, H. S. (2005). "Idiopathic intracranial hypertension presenting with psychiatric symptoms." Journal of Neuropsychiatry Clinical Neuroscience **17**: 426-427.

Dunkley, S. and I. Johnston (2004). "Thrombophilia as a common predisposing factor in pseudotumour cerebri." Blood **103**(5): 1972-3.

Durcan, F., J. Corbett, et al. (1988). "The incidence of pseudotumour cerebri: population studies in Iowa and Louisiana." Archives of Neurology **45**: 875-877.

Esack, A., G. Thompson, et al. (1989). "Benign intracranial hypertension and essential thrombocythaemia." Journal of Neurology, Neurosurgery & Psychiatry **52**: 914-922.

Farb, R. I., I. Vanek, et al. (2003). "Idiopathic intracranial hypertension: the prevalence and morphology of sinovenous stenosis.[see comment]." Neurology. **60**(9): 1418-24.

Finsterer, J., D. Foldy, et al. (2006). "Topiramate resolves headache from pseudotumor cerebri." J Pain Symptom Manage **32**(5): 401-2.

Fishman, R. A. (2002). "Polar bear liver, vitamin A, aquaporins, and pseudotumor cerebri." Ann Neurol **52**(5): 531-3.

Flier, J. S. (2004). "Obesity wars: molecular progress confronts an expanding epidemic." Cell **116**(2): 337-50.

Foley, J. (1955). "Benign Forms of Intracranial Hypertension - "Toxic" and "Otitic" Hydrocephalus." Brain **78**(1): 1-41.

Fried, S. K., M. R. Ricci, et al. (2000). "Regulation of leptin production in humans." Journal of Nutrition **130**: 3127S-3131S.

Friedman, D. I. (2001). "Papilledema and pseudotumor cerebri." Ophthalmology Clinics of North America **14**(1): 129-47, ix.

Friedman, D. I. and D. M. Jacobson (2002). "Diagnostic criteria for idiopathic intracranial hypertension." Neurology. **59**(10): 1492-5.

Friedman, D. I. and E. A. Rausch (2002). "Headache diagnoses in patients with treated idiopathic intracranial hypertension." Neurology **58**(10): 1551-3.

Frisen, L. (1982). "Swelling of the optic nerve head: a staging scheme." Journal of Neurology, Neurosurgery & Psychiatry **45**: 13-18.

Fujiwara, S., Y. Sawamura, et al. (1997). "Idiopathic intracranial hypertension in female homozygous twins." Journal of Neurology, Neurosurgery & Psychiatry **62**: 652-654.

Galvin, J. and G. Van Stavern (2004). "Clinical Characterization of Idiopathic Intracranial Hypertension at the Detroit Medical Centre." Journal of the Neurological Sciences **223**: 157-160.

Garcia, J. P. S., P. T. Garcia, et al. (2004). "A 3-dimensional ultrasound C-scan imaging technique for optic nerve measurements." Ophthalmology **111**(6): 1238-1243.

Geeraerts, T., J. Duranteau, et al. (2008). "Ocular sonography in patients with raised intracranial pressure: the papilloedema revisited." Crit Care **12**(3): 150.

Geeraerts, T., V. F. Newcombe, et al. (2008). "Use of T2-weighted magnetic resonance imaging of the optic nerve sheath to detect raised intracranial pressure." Crit Care **12**(5): R114.

Genizi, J., E. Lahat, et al. (2007). "Childhood-onset idiopathic intracranial hypertension: relation of sex and obesity." Pediatr Neurol **36**(4): 247-9.

Giuseffi, V., M. Wall, et al. (1991). "Symptoms and disease associations in idiopathic intracranial hypertension (pseudotumour cerebri): A case-control study." Neurology **41**: 329-244.

Gjerris, F., P. Soelberg Sorensen, et al. (1985). "Intracranial pressure, conductance to cerebrospinal fluid outflow, and cerebral blood flow in patients with benign intracranial hypertension (pseudotumor cerebri)." Annals of Neurology **17**(2): 158-62.

Glueck, C. J., D. Aregawi, et al. (2005). "Idiopathic intracranial hypertension, polycystic-ovary syndrome, and thrombophilia." Journal of Laboratory & Clinical Medicine **145**(2): 72-82.

Glueck, C. J., S. Iyengar, et al. (2003). "Idiopathic intracranial hypertension: associations with coagulation disorders and polycystic-ovary syndrome." Journal of Laboratory & Clinical Medicine. **142**(1): 35-45.

Green, E. D., M. Maffei, et al. (1995). "The human obese (OB) gene: RNA expression mapping on the physical, cytogenetic and genetic maps of chromosome 7." Genome Research **5**: 5-12.

Greer, M. (1964). "Benign Intracranial Hypertension. V. Menstrual Dysfunction." Neurology **14**: 668-673.

Greer, M. (1965). "Benign Intracranial Hypertension. VI. Obesity." Neurology **15**: 382-388.
Grossmann, W. M. and B. Koeberle (2000). "The dose-response relationship of acetazolamide on the cerebral blood flow in normal subjects." Cerebrovasc Dis **10**(1): 65-9.
Gucer, G. and L. Viernstein (1978). "Long-term intracranial pressure recording in the management of pseudotumour cerebri." Journal of Neurosurgery **49**: 256-263.
Gupta, A. K., M. G. Ganth, et al. (2003). "Modified endoscopic optic nerve decompression in idiopathic intracranial hypertension." J Laryngol Otol **117**(6): 501-2.
Hagan, M. H., P. J. Havel, et al. (1999). "Cerebrospinal fluid and plasma leptin measurements: Covariability with dopamine and cortisol in fasting humans." Journal of Clinical Endocrinology & Metabolism **84**: 3579-3585.
Han, Y., T. J. McCulley, et al. (2008). "No correlation between intraocular pressure and intracranial pressure." Ann Neurol **64**(2): 221-4.
Hansen, H. C. and K. Helmke (1996). "The subarachnoid space surrounding the optic nerves. An ultrasound study of the optic nerve sheath." Surg Radiol Anat **18**(4): 323-8.
Hardie, L., P. Trayhurn, et al. (1997). "Circulating leptin in women: a longitudinal study in the menstrual cycle and during pregnancy." Clinical Endocrinology **47**: 101-106.
Hayes, K. C., H. L. McCombs, et al. (1971). "The fine structure of vitamin A deficiency II. Arachnoid granulations and csf pressure." Brain **94**: 213-224.
Higgins, J., J. Gillard, et al. (2004). "MR Venography in idiopathic intracranial hypertension: unappreciated and misunderstood." Journal of Neurology, Neurosurgery & Psychiatry **75**(4): 621-5.
Higgins, J. and J. Pickard (2004). "Lateral sinus stenoses in idiopathic intracranial hypertension resolving after CSF diversion." Neurology **62**: 1907-1908.
Higgins, J. N., C. Cousins, et al. (2003). "Idiopathic intracranial hypertension: 12 cases treated by venous sinus stenting." Journal of Neurology, Neurosurgery & Psychiatry. **74**(12): 1662-6.
Holladay, J. T. and T. C. Prager (1989). "Snellen equivalent for the Bailey-Lovie acuity chart." Arch Ophthalmol **107**(7): 955.
Hoyt, W. F. and C. L. Knight (1973). "Comparison of congenital disc blurring and incipient papilledema in red-free light--a photographic study." Invest Ophthalmol **12**(4): 241-7.
Hu, K., A. Davis, et al. (2008). "Distinguishing optic disc drusen from papilloedema." BMJ **337**: a2360.
Huang, S. Y., R. E. McCullough, et al. (1988). "Usual clinical dose of acetazolamide does not alter cerebral blood flow velocity." Respir Physiol **72**(3): 315-26.
Hudson, C., S. Shah, et al. (1995). "Scanning laser tomography in benign intracranial hypertension [letter]." Lancet **346**(8987): 1435.
Hung, H. L., L. Y. Kao, et al. (2003). "Ophthalmic features of idiopathic intracranial hypertension." Eye **17**(6): 793-5.
Ireland, B., J. Corbett, et al. (1990). "The search for causes of idiopathic intracranial hypertension: A preliminary case-control study." Archives of Neurology **47**: 315-320.
Ishizu, T., M. Osoegawa, et al. (2005). "Intrathecal activation of the IL-17/IL-8 axis in opticospinal multiple sclerosis." Brain **128**(Pt 5): 988-1002.
Jacobson, D. M., R. Berg, et al. (1999). "Serum vitamin A concentration is elevated in idiopathic intracranial hypertension." Neurology **53**(5): 1114-8.

Jacobson, H. G. and J. H. Shapiro (1964). "Pseudotumor Cerebri." Radiology **82**: 202-10.

Jefferson, A. and J. Clark (1976). "Treatment of benign intracranial hypertension by dehydrating agents with particular reference to the measurement of the blind spot area as a means of recording improvement." J Neurol Neurosurg Psychiatry **39**(7): 627-39.

Johnson, L. N., G. B. Krohel, et al. (1998). "The role of weight loss and acetazolamide in the treatment of idiopathic intracranial hypertension (pseudotumor cerebri)." Ophthalmology **105**(12): 2313-7.

Johnston, I., D. L. Gilday, et al. (1975). "The effects of steroids and steroid withdrawal on CSF absorption. An experimental study in dogs." J Neurosurg **42**: 690-5.

Johnston, I., C. Kollar, et al. (2002). "Cranial venous outflow obstruction in the pseudotumour syndrome: incidence, nature and relevance." J Clin Neurosci **9**(3): 273-8.

Johnston, I., B. Owler, et al. (2007). The Pseudotumour Cerebri Syndrome. Cambridge, UK, Cambridge University Press.

Johnston, I. and A. Paterson (1974). "Benign intracranial hypertension. II. CSF pressure and circulation." Brain **97**(2): 301-12.

Johnston, I., A. Paterson, et al. (1981). "The treatment of benign intracranial hypertension: a review of 134 cases." Surg.Neurol **16**: 218-24.

Kapicioglu, S., E. Gokce, et al. (1997). "Treatment of migraine attacks with a long-acting somatostatin analogue (octreotide, SMS 201-995)." Cephalalgia **17**(1): 27-30.

Kapoor, K. G. (2008). "Do patients with idiopathic intracranial hypertension suffer from hyposmia?" Med Hypotheses **71**(5): 816-7.

Kapoor, K. G. (2008). "Etiology of dizziness, tinnitus, and nausea in idiopathic intracranial hypertension." Medical Hypotheses **71**(2): 310-311.

Karahalios, D. G., H. L. Rekate, et al. (1996). "Elevated intracranial venous pressure as a universal mechanism in pseudotumor cerebri of varying etiologies." Neurology **46**(1): 198-202.

Karam, E. Z. and T. R. Hedges (2005). "Optical coherence tomography of the retinal nerve fibre layer in mild papilloedema and pseudopapilloedema." Br J Ophthalmol **89**(3): 294-8.

Karaman, K., A. Gverovic-Antunica, et al. (2003). "Familial idiopathic intracranial hypertension." Croat Med J **44**(4): 480-4.

Katz, S., D. Klisovic, et al. (2002). "Expression of somatostatin receptors 1 and 2 in human choroid plexus and arachnoid granulations: implications for idiopathic intracranial hypertension." Archives of Ophthalmology **120**(11): 1540.

Keating, J. P. and R. D. Feigin (1970). "Increased intracranial pressure associated with probable vitamin A deficiency in cystic fibrosis." Pediatrics **46**(1): 41-6.

Keltner, J. L. (1988). "Optic nerve sheath decompression. How does it work? Has its time come?" Archives of Ophthalmology **106**(10): 1365-9.

Keltner, J. L., C. A. Johnson, et al. (2000). "Confirmation of visual field abnormalities in the Ocular Hypertension Treatment Study. Ocular Hypertension Treatment Study Group." Archives of Ophthalmology **118**(9): 1187-94.

Kesler, A., M. H. Ellis, et al. (2000). "Idiopathic intracranial hypertension and anticardiolipin antibodies." Journal of Neurology, Neurosurgery & Psychiatry **68**(3): 379-80.

Kesler, A. and N. Gadoth (2001). "Epidemiology of idiopathic intracranial hypertension in Israel." Journal of Neuro-Ophthalmology **21**(1): 12-4.

Kesler, A., Y. Goldhammer, et al. (2001). "Do men with pseudomotor cerebri share the same characteristics as women? A retrospective review of 141 cases." Journal of Neuro-Ophthalmology **21**(1): 15-7.

Kesler, A., Y. Goldhammer, et al. (2004). "The outcome of pseudotumor cerebri induced by tetracycline therapy." Acta Neurol Scand **110**(6): 408-411.

Kesler, A., A. Hadayer, et al. (2004). "Idiopathic intracranial hypertension: Risk of Recurrences." Neurology **63**: 1737-1739.

Kessler, L. A., P. M. Novelli, et al. (1998). "Surgical treatment of benign intracranial hypertension--subtemporal decompression revisited." Surgical Neurology **50**(1): 73-6.

Killer, H. E., G. P. Jaggi, et al. (2006). "The optic nerve: a new window into cerebrospinal fluid composition?" Brain **129**(Pt 4): 1027-30.

Killer, H. E., G. P. Jaggi, et al. (2007). "Cerebrospinal fluid dynamics between the intracranial and the subarachnoid space of the optic nerve. Is it always bidirectional?" Brain **130**(Pt 2): 514-20.

King, J. O., P. J. Mitchell, et al. (1995). "Cerebral venography and manometry in idiopathic intracranial hypertension." Neurology **45**(12): 2224-8.

King, J. O., P. J. Mitchell, et al. (2002). "Manometry combined with cervical puncture in idiopathic intracranial hypertension." Neurology **58**(1): 26-30.

Kirkham, T. H., M. D. Sanders, et al. (1973). "Unilateral papilloedema in benign intracranial hypertension." Can J Ophthalmol **8**(4): 533-8.

Kleinschmidt, J. J., K. B. Digre, et al. (2000). "Idiopathic intracranial hypertension: relationship to depression, anxiety, and quality of life." Neurology **54**(2): 319-24.

Klok, M. D., S. Jakobsdottir, et al. (2007). "The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review." Obes Rev **8**(1): 21-34.

Knapp, C. M. and R. Sampath (2005). "Optic Nerve Sheath Fenestration: A Five Year Audit." Neuro-Ophthalmology **29**(5-6): 173-177.

Korbonits, M., P. J. Trainer, et al. (1997). "Leptin levels do not change acutely with food administration in normal or obese subjects, but are negatively correlated with pituitary-adrenal activity." Clin Endocrinol (Oxf) **46**(6): 751-7.

Krogsaa, B., P. Soelberg Sorensen, et al. (1985). "Ophthalmologic prognosis in benign intracranial hypertension." Acta Ophthalmologica Supplementum **173**: 62-4.

Kupersmith, M., L. Gamell, et al. (1998). "Effects of Weight Loss on the Course of Idiopathic Intracranial Hypertension in Women." Neurology **50**: 1094-1098.

Kupersmith, M. J., L. Gamell, et al. (1998). "Effects of weight loss on the course of idiopathic intracranial hypertension in women." Neurology **50**(4): 1094-8.

Kuzman, M. R., N. Jovanovic, et al. (2008). "Psychiatric symptoms in idiopathic intracranial hypertension." Psychiatry Clin Neurosci **62**(3): 367.

Lampl, Y., Y. Eshel, et al. (2002). "Serum leptin level in women with idiopathic intracranial hypertension." Journal of Neurology, Neurosurgery & Psychiatry. **72**(5): 642-3.

Leaf, D. E. and D. S. Goldfarb (2007). "Mechanisms of action of acetazolamide in the prophylaxis and treatment of acute mountain sickness." J Appl Physiol **102**(4): 1313-22.

Lee, A. G., K. Golnik, et al. (2002). "Sleep apnea and intracranial hypertension in men." Ophthalmology **109**(3): 482-5.

Lee, A. G., M. Pless, et al. (2005). "The use of acetazolamide in idiopathic intracranial hypertension during pregnancy." American Journal of Ophthalmology **139**(5): 855-9.

Lee, M. C., B. Yamini, et al. (2004). "Pseudotumor cerebri patients with shunts from the cisterna magna: clinical course and telemetric intracranial pressure data." Neurosurgery **55**(5): 1094-9.

Lenfeldt, N., L. O. Koskinen, et al. (2007). "CSF pressure assessed by lumbar puncture agrees with intracranial pressure." Neurology **68**(2): 155-8.

Lepore, F. E. (1992). "Unilateral and highly asymmetric papilledema in pseudotumor cerebri." Neurology **42**(3 Pt 1): 676-8.

Levine, D. N. (2000). "Ventricular size in pseudotumor cerebri and the theory of impaired CSF absorption." Journal of the Neurological Sciences **177**(2): 85-94.

Lim, K., M. Kurian, et al. (2004). "Visual Failure without headache in idiopathic intracranial hypertension." Archives of Diseases in Childhood **90**(2): 206-10.

Lindvall-Axelsson, M. and C. Owman (1990). "Actions of sex steroids and corticosteroids on rabbit choroid plexus as shown by changes in transport capacity and rate of cerebrospinal fluid formation." Neurol Res **12**(3): 181 - 6.

Lipton, H. L. and P. E. Michelson (1972). "Pseudotumor cerebri syndrome without papilledema." Jama **220**(12): 1591-2.

Liu, G. T., J. S. Glaser, et al. (1994). "High-dose methylprednisolone and acetazolamide for visual loss in pseudotumour cerebri." Am J Ophthalmol **118**: 88-96.

Lochhead, J. and J. S. Elston (2003). "Doxycycline induced intracranial hypertension." British Medical Journal **326**: 641-2.

Lorenzen, S. E. (1966). "Drusen of the optic disc: A clinical and genetic study
" Acta Ophthal.Suppl **90**: 1-19.

Lueck, C. and G. McIlwaine (2005). "Interventions for idiopathic intracranial hypertension." Cochrane Database of Systematic Reviews **3**.

Lueck, C. J. and G. G. McIlwaine (2002). "Idiopathic Intracranial Hypertension." Practical Neurology **2**: 262-271.

Mackenzie, P. J. and G. A. Cioffi (2008). "Vascular anatomy of the optic nerve head." Can J Ophthalmol **43**(3): 308-12.

Maedler, K., P. Sergeev, et al. (2002). "Glucose-induced beta cell production of IL-1beta contributes to glucotoxicity in human pancreatic islets." J Clin Invest **110**(6): 851-60.

Malm, J., B. Kristensen, et al. (1992). "CSF hydrodynamics in idiopathic intracranial hypertension: a long-term study." Neurology **42**(4): 851-8.

Marcelis, J. and S. D. Silberstein (1991). "Idiopathic intracranial hypertension without papilledema." Archives of Neurology **48**(4): 392-9.

Marcus, D. M., J. Lynn, et al. (2001). "Sleep disorders: a risk factor for pseudotumor cerebri?" J Neuroophthalmol **21**(2): 121-3.

Martins, A. (1973). "Resistance to drainage of cerebrospinal fluid: clinical measurement and significance." Journal of Neurology, Neurosurgery & Psychiatry **36**: 313-318.

Matharu, M. S., M. J. Levy, et al. (2004). "Subcuteneous octreotide in cluster headache: randomized, placebo-controlled, double-blind crossover study." Ann Neurol **56**(4): 488-94.

Mathew, N., K. Ravishankar, et al. (1996). "Co-existence of migraine and idiopathic intracranial hypertension without papilledema." Neurology **46**: 1226-1230.

McCarthy, K. D. and D. J. Reed (1974). "The effect of acetazolamide and furosemide on cerebrospinal fluid production and choroid plexus carbonic anhydrase activity." J Pharmacol Exp Ther **189**(1): 194-201.

McGirt, M. J., G. Woodworth, et al. (2004). "Cerebrospinal fluid shunt placement for pseudotumor cerebri-associated intractable headache: predictors of treatment response and an analysis of long-term outcomes." J Neurosurg **101**(4): 627-32.

Meier, U. and A. M. Gressner (2004). "Endocrine regulation of energy metabolism: Review of pathobiological and clinical chemical aspects of Leptin, Ghrelin, Adiponectin and Resistin." Clinical Chemistry **50**(9): 1511-26.

Menendez, C., R. Baldelli, et al. (2000). "The in vitro secretion of human leptin is gender-dependent but independent of the body mass index of the donors." European Journal of Endocrinology **143**(5): 711-4.

Mercer, J. G., N. Hoggard, et al. (1996). "Coexpression of leptin receptor and preproneuropeptide Y mRNA in arcuate nucleus of mouse hypothalamus." J Neuroendocrinol **8**(10): 733-5.

Messinis, I. E., I. Papageorgiou, et al. (2001). "Oestradiol plus progesterone treatment increases seum leptin concentrations in normal women." Human Reproduction **16**(9): 1827-1832.

Mezaal, M. and M. Saadah (2005). "Idiopathic intracranial hypertension in Dubai: nature and prognosis." Acta Neurologica Scandinavica **112**(5): 298-302.

Mollan, S. P., A. K. Ball, et al. (2009). "Idiopathic intracranial hypertension associated with iron deficiency anaemia: a lesson for management." Eur Neurol **62**(2): 105-8.

Morash, B., A. Li, et al. (1999). "Leptin gene expression in the brain and pituitary gland." Endocrinology **140**(12): 5995-8.

Morton, G. J., J. E. Blevins, et al. (2005). "Leptin action in the forebrain regulates the hindbrain response to satiety signals." Journal of Clinical Investigation **115**(3): 703-710.

Moser, F. G., S. K. Hilal, et al. (1988). "MR imaging of pseudotumor cerebri." AJR. American Journal of Roentgenology **150**(4): 903-9.

Mulholland, D. A., J. J. Craig, et al. (1998). "Use of scanning laser ophthalmoscopy to monitor papilloedema in idiopathic intracranial hypertension." British Journal of Ophthalmology **82**(11): 1301-5.

Nadkarni, T., H. L. Rekate, et al. (2004). "Resolution of pseudotumour cerebri after bariatric surgery for related obesity." Journal of Neurosurgery **101**: 878-880.

Nam, S., J. Kratzsch, et al. (2001). "cerebrospinal fluid and plasma concentrations of leptin, NPY and alpha-MSH in obese women and their relationship to negative energy balance." Journal of Clinical Endocrinology & Metabolism **86**: 4849-4853.

Neville, B. G. and J. Wilson (1970). "Benign intracranial hypertension following corticosteroid withdrawal in childhood." British Medical Journal **3**(722): 554-6.

Neville, L. and R. A. Egan (2005). "Frequency and amplitude of elevation of cerebrospinal fluid resting pressure by the Valsalva maneuver." Can J Ophthalmol **40**(6): 775-7.

Newborg, B. (1974). "Pseudotumor cerebri treated by rice reduction diet." Archives of Internal Medicine **133**(5): 802-7.

Nisoli, E., C. Tonello, et al. (1996). "Expression of nerve growth factor in brown adipose tissue: implications for thermogenesis and obesity." Endocrinology **137**(2): 495-503.

Nonne, M. (1904). "Uber Falle vom Symptomkomplex "Tumor Cerebir" mit Ausgang in Heilling (Pseudotumour Cerebri)." Dtsch. Zeit. f. Nervenheil **27**: 169-216.

Ooi, K. G., G. Galatowicz, et al. (2006). "Multiplex cytokine detection versus ELISA for aqueous humor: IL-5, IL-10, and IFNgamma profiles in uveitis." Invest Ophthalmol Vis Sci **47**(1): 272-7.

Orcutt, J. C., N. G. Page, et al. (1984). "Factors affecting visual loss in benign intracranial hypertension." Ophthalmology **91**(11): 1303-12.

Orefice, G., L. Celentano, et al. (1992). "Radioisotopic cisternography in benign intracranial hypertension of young obese women. A seven-case study and pathogenetic suggestions." Acta Neurologica **14**(1): 39-50.

Orefice, G., G. De Joanna, et al. (1995). "Case Report: Benign Intracranial Hypertension: a non-thrombotic complication of the primary antiphospholipid syndrome?" Lupus **4**: 324-326.

Ossoinig, K. C. (1979). "Standardised echography: basic principles, clinical applications and results." Int Ophth Clin **19**: 127-210.

Ostlund, R. E., Jr., J. W. Yang, et al. (1996). "Relation between plasma leptin concentration and body fat, gender, diet, age, and metabolic covariates." J Clin Endocrinol Metab **81**(11): 3909-13.

Owler, B. K., G. Parker, et al. (2003). "Pseudotumor cerebri syndrome: venous sinus obstruction and its treatment with stent placement." Journal of Neurosurgery **98**(5): 1045-55.

Pagan, F. L., L. Restrepo, et al. (2002). "A new drug for an old condition?" Headache **42**(7): 695-6.

Panagiotakos, D. B., C. Pitsavos, et al. (2005). "The implication of obesity and central fat on markers of chronic inflammation: The ATTICA study." Atherosclerosis **183**(2): 308-15.

Panagopoulos, G. N., S. N. Deftereos, et al. (2007). "Octreotide: A therapeutic option for idiopathic intracranial hypertension." Neurology, Neurophysiology and Neuroscience **1**: 1-6.

Park, H. S., J. Y. Park, et al. (2005). "Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6." Diabetes Res Clin Pract **69**(1): 29-35.

Parness-Yossifon, R., D. Margalit, et al. (2008). "Behavioral disorders in children with idiopathic intracranial hypertension." J Child Neurol **23**(4): 447-50.

Paterson, R., N. DePasquale, et al. (1961). "Pseudotumour cerebri." Medicine **40**: 85-99.

Pelleymounter, M. A., M. B. Baker, et al. (1999). "Does estradiol mediate leptin's effects on adiposity and body weight?" American Journal of Physiology **276**(5): E955-63.

Pelli, D. G., J. G. Robson, et al. (1988). "The design of a new letter chart for measuring contrast sensitivity." Clinical Vision Sciences **2**: 187-199.

Plewe, G., J. Beyer, et al. (1984). "Long-acting and selective suppression of growth factor hormone secretion by somatostatin analogue SMS 201-995 in acromegaly." Lancet **2**: 782-4.

Pollay, M. and K. Welch (1962). "The function and structure of canine arachnoid villi." J Surg Res **2**: 307-11.

Purvin, V. A., A. Kawasaki, et al. (2000). "Papilledema and obstructive sleep apnea syndrome." Arch Ophthalmol **118**(12): 1626-30.

Quincke, H. (1893). "Meningitis Serosa." Sammi. Klin. Votr **67**.

Rabinowicz, I. M., I. Ben-Sira, et al. (1968). "Preservation of visual function in papilloedema: Observed for 3 to 6 years in cases of benign intracranial hypertension." British Journal of Ophthalmology **52**: 236-241.

Radhakrishnan, K., A. K. Thacker, et al. (1993). "Epidemiology of idiopathic intracranial hypertension: a prospective and case-control study." Journal of the Neurological Sciences **116**(1): 18-28.

Rasmussen, T. and D. R. Gulati (1962). "Cortisone in the treatment of post-operative cerebral oedema." Journal of Neurosurgery **19**: 535-544.

Reid, A. C. and J. A. Thomson (1981). "Absence of significant endocrine deficiencies in benign intracranial hypertension." Journal of Neurology, Neurosurgery & Psychiatry **44**(8): 731-4.

Rodrigues, A. M., R. B. Radominski, et al. (2002). "The cerebrospinal fluid / serum leptin ratio during pharmacological therapy for obesity." Journal of Clinical Endocrinology & Metabolism **87**: 1621-1626.

Rohner-Jeanrenaud, F. and B. Jeanrenaud (1996). "Obesity, leptin and the brain." New England Journal of Medicine **334**(5): 324-5.

Rose, A. and D. D. Matson (1967). "Benign Intracranial Hypertension in children." Pediatrics **39**(2): 227-237.

Rosenbaum, M. and R. L. Leibel (1999). "Role of gonadal steroids in the sexual dimorphisms in body composition and circulating concentrations of leptin." Journal of Clinical Endocrinology & Metabolism **84**(6): 1784-89.

Rosenbaum, M., M. Nicolson, et al. (1996). "Effects of gender, body composition, and menopause on plasma concentrations of leptin." Journal of Clinical Endocrinology & Metabolism **81**(9): 3424-27.

Rosenberg, M. M., J. J. Corbett, et al. (1993). "Cerebrospinal fluid diversion procedures in pseudotumour cerebri." Neurology **43**: 1071-1072.

Rowe, F. and C. Noonan (2002). "The prevalence of overweight and obesity in a childhood population of idiopathic intracranial hypertension." Neuro-Ophthalmology **28**(2): 87-93.

Rowe, F. and N. Sarkies (1998). "Assessment of visual function in idiopathic intracranial hypertension: a prospective study." Eye **12**: 111-118.

Rubin, R. C., E. S. Henderson, et al. (1966). "The production of cerebrospinal fluid in man and its modification by acetazolamide." Journal of Neurosurgery **25**(4): 430-6.

Rush, J. A. (1980). "Pseudotumor cerebri: clinical profile and visual outcome in 63 patients." Mayo Clin Proc **55**(9): 541-6.

Sahs, A. L. and R. J. Joynt (1956). "Brain swelling of unknown cause." Neurology **6**(11): 801-3.

Sajjadi, S. A., M. H. Harirchian, et al. (2006). "The relation between intracranial and intraocular pressures: study of 50 patients." Ann Neurol **59**(5): 867-70.

Sanders, M. D. (1970). "A classification of papilloedema based on a fluorescein angiographic study of 69 cases." Trans Ophthalmol Soc U K **89**: 177-97.

Sanders, M. D. (1997). "The Bowman Lecture. Papilloedema: 'the pendulum of progress'." Eye **11 (Pt 3)**: 267-94.

Sanders, T. E., A. J. Gay, et al. (1970). "Drusen of the optic disk: Hemorrhagic complications." Transactions American Ophthalmological Society **68**: 186-218.

Sartipy, P. and D. J. Loskutoff (2003). "Monocyte chemoattractant protein 1 in obesity and insulin resistance." Proc Natl Acad Sci U S A **100**(12): 7265-70.

Schirmer, C. M. and T. R. Hedges, 3rd (2007). "Mechanisms of visual loss in papilledema." Neurosurg Focus **23**(5): E5.

Schoeman, J. F. (1994). "Childhood pseudotumor cerebri: clinical and intracranial pressure response to acetazolamide and furosemide treatment in a case series." J Child Neurol **9**(2): 130-4.

Schwartz, M. W., E. Peskind, et al. (1996). "Cerebrospinal fluid leptin levels: relationship to plasma levels and to adiposity in humans." Nature Medicine **2**(5): 589-593.

Scott, I. U., R. M. Siatkowski, et al. (1997). "Idiopathic intracranial hypertension in children and adolescents." Am J Ophthalmol **124**(2): 253-5.

Seckl, J. (2004). "Pondering obesity: Therapeutic targets in brain and fat." Journal of the Royal College of Physicians of Edinburgh **34**: 177-179.

Seckl, J. and S. Lightman (1988). "Cerebrospinal fluid neurohypophysial peptides in benign intracranial hypertension." Journal of Neurology, Neurosurgery & Psychiatry **51**: 1538-1541.

Selhorst, J. B., K. Kulkantrakorn, et al. (2000). "Retinol-binding protein in idiopathic intracranial hypertension (IIH)." Journal of Neuro-Ophthalmology **20**(4): 250-2.

Shah, V. A., S. Fung, et al. (2007). "Idiopathic intracranial hypertension." Ophthalmology **114**(3): 617.

Shah, V. A., R. H. Kardon, et al. (2008). "Long-term follow-up of idiopathic intracranial hypertension: the Iowa experience." Neurology **70**(8): 634-40.

Silberstein, S. D., E. Loder, et al. (2006). "The impact of migraine on daily activities: effect of topiramate compared with placebo." Curr Med Res Opin **22**(6): 1021-9.

Sinclair, A. J., M. A. Burdon, et al. (2009). The Birmingham Weight Loss in Idiopathic Intracranial Hypertension and Intracranial Pressure Study. American Academy of Neurology 61st Annual Meeting: Abstract LB2.002. Seattle, USA.

Sinclair, N., N. Assaad, et al. (2002). "Pseudotumour cerebri occurring in association with the Chiari malformation." J Clin Neurosci **9**(1): 99-101.

Sorensen, P. S., F. Gjerris, et al. (1986). "Endocrine studies in patients with pseudotumour cerebri." Archives of Neurology **43**: 902-906.

Sorensen, P. S., M. Hammer, et al. (1982). "Cerebrospinal fluid vasopressin in benign intracranial hypertension." Neurology **32**: 1255-9.

Sorensen, P. S., B. Krogsaa, et al. (1988). "Clinical course and prognosis of pseudotumor cerebri. A prospective study of 24 patients." Acta Neurol Scand **77**(2): 164-72.

Sorensen, P. S., A. M. Thomsen, et al. (1986). "Persistent disturbances of cognitive functions in patients with pseudotumour cerebri." Acta Neurologica Scandinavica **73**(3): 264-8.

Speake, T., C. Whitwell, et al. (2001). "Mechanisms of CSF secretion by the choroid plexus." Microsc Res Tech **52**(1): 49-59.

Spoor, T. C., J. G. McHenry, et al. (1994). "Optic nerve sheath decompression with adjunctive mitomycin and Molteno device implantation [letter]." Archives of Ophthalmology **112**(1): 25-6.

Stiebel-Kalish, H., Y. Kalish, et al. (2006). "Puberty as a risk factor for less favorable visual outcome in idiopathic intracranial hypertension." Am J Ophthalmol **142**(2): 279-83.

Straczkowski, M., S. Dzienis-Straczkowska, et al. (2002). "Plasma interleukin-8 concentrations are increased in obese subjects and related to fat mass and tumor necrosis factor-alpha system." J Clin Endocrinol Metab **87**(10): 4602-6.

Straczkowski, M., I. Kowalska, et al. (2006). "Plasma levels of soluble tumor necrosis factor-alpha receptors are related to total and LDL-cholesterol in lean, but not in obese subjects." Cardiovasc Diabetol **5**: 14.

Subramanian, P., N. Goldenberg-Cohen, et al. (2004). "Ghrelin levels are normal in obese patients with idiopathic intracranial hypertension (pseudotumour cerebri)." American Journal of Ophthalmology **138**(1): 109-113.

Sugerman, H., E. DeMaria, et al. (1997). "Increased intra-abdominal pressure and cardiac filling pressures in obesity-associated pseudotumour cerebri." Neurology **49**: 507-511.

Sugerman, H. J., W. L. Felton, 3rd, et al. (1999). "Gastric surgery for pseudotumor cerebri associated with severe obesity." Annals of Surgery **229**(5): 634-40; discussion 640-2.

Sussman, J., M. Leach, et al. (1997). "Potentially prothrombotic abnormalities of coagulation in benign intracranial hypertension." Journal of Neurology, Neurosurgery & Psychiatry **62**(3): 229-33.

Sylaja, P. N., N. V. Ahsan Moosa, et al. (2003). "Differential diagnosis of patients with intracranial sinus venous thrombosis related isolated intracranial hypertension from those with idiopathic intracranial hypertension." Journal of the Neurological Sciences. **215**(1-2): 9-12.

Symonds, C. (1956). "Otitic Hydrocephalus." Neurology **6**(10): 681-685.

Tabassi, A., A. H. Salmasi, et al. (2005). "Serum and CSF vitamin A concentrations in idiopathic intracranial hypertension." Neurology **64**(11): 1893-6.

Tae Wan Kim, H. K. C., Sang In Khwarg, Jeong-Min Hwang, Hee Jin Yang, (2008). "Obesity may not be a risk factor for idiopathic intracranial hypertension in Asians." European Journal of Neurology **15**(8): 876-879.

Tartaglia, L., M. Dembski, et al. (1995). "Identification and expression cloning of a leptin receptor OB-R. Cell." Nature Medicine **83**: 1263-71.

Testa, L., D. Mittino, et al. (2008). "Cluster-like headache and idiopathic intracranial hypertension: a case report." J Headache Pain **9**(3): 181-3.

Thambisetty, M., P. J. Lavin, et al. (2007). "Fulminant idiopathic intracranial hypertension." Neurology **68**(3): 229-32.

Thapa, R., A. Ghosh, et al. (2009). "Childhood hepatitis A virus infection complicated by pseudotumor cerebri." South Med J **102**(2): 204-5.

Thapa, R., D. Mallick, et al. (2009). "Pseudotumor cerebri in childhood hepatitis E virus infection." Headache **49**(4): 610-1.

Thong, F. S. L., C. McLean, et al. (2000). "Plasma leptin in female athletes: relationship with body fat, reproductive, nutritional and endocrine factors." Journal of Applied Physiology **88**: 2037-2044.

Tilg, H. and A. R. Moschen (2006). "Adipocytokines: mediators linking adipose tissue, inflammation and immunity." Nat Rev Immunol **6**(10): 772-83.

Torbey, M. T., R. G. Geocadin, et al. (2004). "Utility of CSF pressure monitoring to identify idiopathic intracranial hypertension without papilledema in patients with chronic daily headache." Cephalalgia **24**(6): 495-502.

Toscano, V., G. Sancesario, et al. (1991). "Cerebrospinal fluid estrone in pseudotumour cerebri: a change in cerebral steroid hormone metabolism?" Journal of Endocrinological Investigation **14**: 81-6.

Tschirgi, R. D., R. W. Frost, et al. (1954). "Inhibition of cerebrospinal fluid formation by a carbonic anhydrase inhibitor, 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide (diamox)." Proc Soc Exp Biol Med **87**(2): 373-6.

Tso, M. O. and S. S. Hayreh (1977). "Optic disc edema in raised intracranial pressure. III. A pathologic study of experimental papilledema." Arch Ophthalmol **95**(8): 1448-57.

Tso, M. O. and S. S. Hayreh (1977). "Optic disc edema in raised intracranial pressure. IV. Axoplasmic transport in experimental papilledema." Arch Ophthalmol **95**(8): 1458-62.

Tso, M. O. M. and B. S. Fine (1976). "Electron Microscopic study of papilloedema in man." Am J Ophthalmol **82**: 424-434.

Tugal, O., R. Jacobson, et al. (1994). "Recurrent benign intracranial hypertension due to iron deficiency anemia. Case report and review of the literature." Am J Pediatr Hematol Oncol **16**(3): 266-70.

Van Heek, M., D. S. Compton, et al. (1997). "Diet-induced obese mice develop peripheral, but not central, resistance to leptin." Journal of Clinical Investigation **99**: 385-390.

Vartzelis, G., D. Lancaster, et al. (2009). "Intracranial hypertension in pediatric patients with acute lymphoblastic leukemia." Pediatr Blood Cancer **52**(3): 418-20.

Verplanck, M., D. I. Kaufman, et al. (1988). "Electrophysiology versus psychophysics in the detection of visual loss in pseudotumor cerebri." Neurology **38**(11): 1789-92.

Vieira, D. S., M. R. Masruha, et al. (2008). "Idiopathic intracranial hypertension with and without papilloedema in a consecutive series of patients with chronic migraine." Cephalalgia **28**(6): 609-13.

Vogh, B. P. and M. R. Langham, Jr. (1981). "The effect of furosemide and bumetanide on cerebrospinal fluid formation." Brain Res **221**(1): 171-83.

Volcy-Gomez, M. and C. S. Uribe (2004). "[Headaches in idiopathic intracranial hypertension. A review of ten years in a Columbian hospital]." Revista de Neurologia **39**(5): 419-23.

Volcy, M. and S. J. Tepper (2006). "Cluster-like headache secondary to idiopathic intracranial hypertension." Cephalalgia **26**(7): 883-6.

Von Graefe, A. (1860). "Complications of optic neuritis with cerebral disease." Arch Ophthalmol **7**: 58.

Vozarova, B., C. Weyer, et al. (2001). "Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion." Obes Res **9**(7): 414-7.

Walker, R. W. (2001). "Idiopathic intracranial hypertension: any light on the mechanism of the raised pressure?" Journal of Neurology, Neurosurgery & Psychiatry **71**(1): 1-5.

Wall, M. (1986). "Contrast sensitivity testing in pseudotumor cerebri." Ophthalmology **93**(1): 4-7.

Wall, M. (1990). "The headache profile of idiopathic intracranial hypertension." Cephalalgia **10**(6): 331-5.

Wall, M. (1995). "Idiopathic intracranial hypertension." Seminars in Ophthalmology **10**(3): 251-9.

Wall, M., M. D. Conway, et al. (1991). "Evaluation of sensitivity and specificity of spatial resolution and Humphrey automated perimetry in pseudotumor cerebri patients and normal subjects." Investigative Ophthalmology & Visual Science **32**(13): 3306-12.

Wall, M., J. D. Dollar, et al. (1995). "Idiopathic intracranial hypertension: Lack of histological evidence for cerebral oedema." Archives of Neurology **52**: 141-145.

Wall, M. and D. George (1991). "Idiopathic intracranial hypertension. A prospective study of 50 patients." Brain **114**: 155-180.

Wall, M., S. D. Silberstein, et al. (2001). "Headache associated with abnormalities in intracranial structure or function: High cerebrospinal fluid pressure headache and brain tumour." In Wolff's Headache and other head pain, Seventh Edition, Oxford University Press.

Wall, M. and W. N. White, 2nd (1998). "Asymmetric papilledema in idiopathic intracranial hypertension: prospective interocular comparison of sensory visual function." Investigative Ophthalmology & Visual Science **39**(1): 134-42.

Wang, S. J., S. D. Silberstein, et al. (1998). "Idiopathic intracranial hypertension without papilledema: a case-control study in a headache center." Neurology **51**(1): 245-9.

Ware, J. E., M. Kosinski, et al. (2000). How to Score Version Two of the SF-36 Health Survey, Quality Metric, Incorporated.

Warner, J. E. A., P. S. Bernstein, et al. (2002). "Vitamin A in the cerbrospinal fluid of patients with and without idiopathic intracranial hypertension." Annals of Neurology **52**: 647-650.

Warner, J. E. A. and B. J. Katz (2005). "Metamorphosia as an initial complaint of idiopathic intracranial hypertension." Archives of Ophthalmology **123**(7): 1003-1996.

Weed, L. H. (1914). "The pathways of escape from the subarachnoid spaces from the subarachnoid space with particular reference to the arachnoid villi." J Med Res **31**: 51-9.

Weigle, D. S., P. B. Duell, et al. (1997). "Effect of fasting, refeeding, and dietary fat restriction on plasma leptin levels." J Clin Endocrinol Metab **82**(2): 561-5.

Weisberg, S. P., D. McCann, et al. (2003). "Obesity is associated with macrophage accumulation in adipose tissue." J Clin Invest **112**(12): 1796-808.

Wellen, K. E. and G. S. Hotamisligil (2005). "Inflammation, stress, and diabetes." J Clin Invest **115**(5): 1111-9.

Welt, C. K., J. L. Chan, et al. (2004). "Recombinant human leptin in women with hypothalamic amenorrhea." New England Journal of Medicine **351**(10): 987-97.

Werner, E. B. (1991). Manual of Visual Fields. Edinburgh, Churchill Livingstone.

White, D. P., C. W. Zwillich, et al. (1982). "Central sleep apnea. Improvement with acetazolamide therapy." Arch Intern Med **142**(10): 1816-9.

Williams, G., J. A. Ball, et al. (1987). "Analgesic effects of somatostatin analogue (octreotide) in headache associated with pituatory tumors." British Medical Journal **295**: 247-8.

Winner, P. and L. Bello (1996). "Idiopathic intracranial hypertension in a young child without visual symptoms or signs." Headache **36**(9): 574-6.

Wolfe, B. E., D. C. Jimerson, et al. (2004). "Effect of dieting on plasma leptin, soluble leptin receptor, adiponectin and resistin levels in healthy volunteers." Clinical Endocrinology **61**: 332-338.

Wong, M., J. Licinio, et al. (2004). "Simulteneous and continuous 24-hour plasma and cerebrospinal fluid leptin measurements: Dissociation of concentrations in central and peripheral compartments." Journal of Clinical Endocrinology & Metabolism **89**(1): 258-265.

Wraige, E., C. Chandler, et al. (2002). "Idiopathic intracranial hypertension: is papilloedema inevitable?" Archives of Disease in Childhood **87**(3): 223-4.

Wright, E. M. (1978). "Transport processes in the formation of the cerebrospinal fluid." Rev Physiol Biochem Pharmacol **83**: 3-34.

Yabe, I., F. Moriwaka, et al. (2000). "Incidence of idiopathic intracranial hypertension in Hokkaido, the northernmost island of Japan." Journal of Neurology **247**(6): 474-5.

Yenice, O. and A. Temel (2005). "Evaluation of two Humphrey perimetry programs: full threshold and SITA standard testing strategy for learning effect." Eur J Ophthalmol **15**(2): 209-12.

You, Q., L. Xu, et al. (2008). "Prevalence of crowded optic discs in adult Chinese. The Beijing Eye Study." Graefe's Archive for Clinical and Experimental Ophthalmology **246**(9): 1291-1293.

Zigmond, A. S. and R. P. Snaith (1983). "The hospital anxiety and depression scale." Acta Psychiatr Scand **67**(6): 361-70.

APPENDIX 1

IIH Trial Data Collection Forms

IIH Trial

Main randomisation
BASELINE DATA

Part 1: PATIENT DETAILS

Patient's initials: .....

Hospital Number: .....

Date of Birth (dd/mmm/yyyy): ...../...../.....

HEIGHT: (centimetres)

WEIGHT: (kilogram)

DATE: ...../...../.....

Ethnic Group (tick one only)

White
- British ☐
- Irish ☐
- Other White ☐

Black/ Black British
- Caribbean ☐
- African ☐
- Other Black ☐

Asian/ Asian British
- Indian ☐
- Pakistani ☐
- Bangladeshi ☐
- Other Asian ☐

Mixed
- Mixed White/ Black Caribbean ☐
- Mixed White/ Black African ☐
- Mixed White/ Asian ☐
- Other Mixed Background ☐

Chinese or Other Ethnic Group
- Chinese ☐
- Any Other ☐

Part 2: PATIENT'S MEDICAL DETAILS:

1. Pre-existing **ocular** conditions? YES [ ] NO [ ]
Details:

2. Known **neurological** conditions? YES [ ] NO [ ]
Details:

3. Relevant **current medication**? YES [ ] NO [ ]
Details:

4. **PREVIOUS MEDICATION**:

	YES	NO	Unknown	Details:
a. Antibiotic use in previous six months?	[ ]	[ ]	[ ]	
b. Hormonal medication? (Contraceptives / HRT / corticosteroids/ Growth Hormone or other)	[ ]	[ ]	[ ]	
c. Vitamin A or derivatives?	[ ]	[ ]	[ ]	
d. Lithium?	[ ]	[ ]	[ ]	

5. Other relevant **medical / surgical history:**

		Yes	No	Comment
6. **Imaging studies**:	MRI / CT brain scan normal?	[ ]	[ ]	
	Venogram / angiography normal?	[ ]	[ ]	
7. Baseline **blood tests** normal?		[ ]	[ ]	
8. Elevated **CSF** opening **pressure?** (if lumbar puncture performed in lateral decubitus position)		[ ]	[ ]	**Recorded CSF pressure(cm H_20):**

Part 3: PATIENT'S SYMPTOMS

	YES	NO	Detail:
Headache	[ ]	[ ]	
			Enter patient-assessed **pain score** (1= no pain, 10 = pain as bad as it can be):
Tinnitus / intracranial noises (state right or left if applicable)	[ ]	[ ]	
Disturbance of sense of smell	[ ]	[ ]	
Visual loss	[ ]	[ ]	
Diplopia	[ ]	[ ]	
Visual obscurations	[ ]	[ ]	
Other	[ ]	[ ]	

ATTACH ALL COMPLETED QUESTIONNAIRES

Part 4: VISUAL ASSESSMENT

Contrast sensitivity *(please circle the number, on each grid, nearest to the faintest triplet for which 2 of the 3 letters are named correctly. Note that actual letter sequences may vary)*

LEFT EYE				RIGHT EYE				BINOCULAR			
0.00	HSN	DSN	0.15	0.00	HSN	DSN	0.15	0.00	HSN	DSN	0.15
0.30	CKR	ZVR	0.45	0.30	CKR	ZVR	0.45	0.30	CKR	ZVR	0.45
0.60	NDC	OSK	0.75	0.60	NDC	OSK	0.75	0.60	NDC	OSK	0.75
0.90	OZK	VHZ	1.05	0.90	OZK	VHZ	1.05	0.90	OZK	VHZ	1.05
1.20	NHO	NRD	1.35	1.20	NHO	NRD	1.35	1.20	NHO	NRD	1.35
1.50	VRC	OVH	1.65	1.50	VRC	OVH	1.65	1.50	VRC	OVH	1.65
1.80	CDS	NDC	1.95	1.80	CDS	NDC	1.95	1.80	CDS	NDC	1.95
2.10	KVC	OHR	2.25	2.10	KVZ	OHR	2.25	2.10	KVZ	OHR	2.25

	LEFT eye	RIGHT eye	Comments
LogMAR			
Humphrey Perimetry: Mean Deviation MD			
Pattern Standard Deviation PSD			
Papilloedema	Present [ ] Absent [ ]	Present [ ] Absent [ ]	
Retinal photographs taken? **** Attach photographs where available ****	Yes [ ] No [ ]	Yes [ ] No [ ]	

- ***ATTACH COPIES OF HUMPHREY PERIMETRY****

- ***Part 5: CONTACT DETAILS***

Name / Position of clinician completing form	Telephone number	Fax number

Please place the completed form and attachments in the envelope provided and leave for collection as arranged, or post to Dr Alex Ball, Department of Neurology, DGM Building, City Hospital, Dudley Road, Birmingham B18 7QH.

Main randomisation VISIT 2
(3 MONTHS Post-Randomisation)

Part 1: PATIENT DETAILS:

Patient's Initials: .....

Hospital Number: .....

Date of Birth (dd/mmm/yyyy): ...../...../.....

TRIAL NUMBER [ ] **WEIGHT** (kilogram) [ ] **DATE** [ ]

Part 2: TREATMENT:

Initial treatment randomisation

Acetazolamide [ ] [ ] **No Acetazolamide**

(Please tick one and complete appropriate sections)

Initial treatment = acetazolamide:	**Initial treatment = NO acetazolamide:**
i. Still taking acetazolamide? (please tick) **Yes [ ]** **(complete sections ii to iv below)** **No [ ]** **(complete section v below)**	i. Has acetazolamide been added? (please tick) **Yes [ ]** **(complete sections ii to iv below)** **No [ ]** **(Go to part 3)**
ii.Current Dose:	ii. Date commenced acetazolamide (if applicable): ____/____/_____
iii. Has dose been changed? (please tick) yes [ ] no [ ]	iii. Current dose (if applicable):
iv. Reason for dose change (if known)	
v. **Reason(s) for stopping acetazolamide** **Please tick *all that apply* from the list below:**	iv**. Reasons for adding acetazolamide:** **Please tick *all that apply* from the list below**
Adverse effects of medication [ ] Details:	Worsening visual field [ ]
Patient preference [ ] Details:	Worsened disc appearance [ ]
Pregnancy or planned pregnancy [ ] Details:	Reduced acuity [ ]
Other reason [ ] Details:	Development of afferent pupillary defect [ ]
	Headaches failing to resolve [ ]
	New visual obscurations [ ]
	Worsening tinnitus [ ]
	Worsening impairment of colour vision [ ]
	Other (please give details below) [ ]

Part 3: PATIENT'S SYMPTOMS

	YES	NO	Detail:
Headache	[ ]	[ ]	
Enter patient-assessed **pain score** (1= no pain, 10 = pain as bad as it can be):			
Tinnitus / intracranial noises	[ ]	[ ]	
Visual loss	[ ]	[ ]	
Diplopia	[ ]	[ ]	
Visual obscurations	[ ]	[ ]	
Other	[ ]	[ ]	

ATTACH ALL COMPLETED QUESTIONNAIRES

Part 4: VISUAL ASSESSMENT

Contrast sensitivity *(please circle the number, on each grid, nearest to the faintest triplet for which 2 of the 3 letters are named correctly. Note that actual letter sequences may vary)*

LEFT EYE

0.00	HSN	DSN	0.15
0.30	CKR	ZVR	0.45
0.60	NDC	OSK	0.75
0.90	OZK	VHZ	1.05
1.20	NHO	NRD	1.35
1.50	VRC	OVH	1.65
1.80	CDS	NDC	1.95
2.10	KVC	OHR	2.25

RIGHT EYE

0.00	HSN	DSN	0.15
0.30	CKR	ZVR	0.45
0.60	NDC	OSK	0.75
0.90	OZK	VHZ	1.05
1.20	NHO	NRD	1.35
1.50	VRC	OVH	1.65
1.80	CDS	NDC	1.95
2.10	KVZ	OHR	2.25

BINOCULAR

0.00	HSN	DSN	0.15
0.30	CKR	ZVR	0.45
0.60	NDC	OSK	0.75
0.90	OZK	VHZ	1.05
1.20	NHO	NRD	1.35
1.50	VRC	OVH	1.65
1.80	CDS	NDC	1.95
2.10	KVZ	OHR	2.25

	LEFT eye	RIGHT eye	Comments
LogMAR			
Humphrey Perimetry: Mean Deviation MD			
Pattern Standard Deviation PSD			
Papilloedema	Present [ ] Absent [ ]	Present [ ] Absent [ ]	
Frisen Grade: (see photographic guide)	……..	……..	
Retinal photographs taken? ***Attach photographs where available***	*Yes [ ] No [ ]*	*Yes [ ] No [ ]*	

ATTACH COPIES OF HUMPHREY PERIMETRY

- **Is surgical intervention required for this patient?** **YES [ ]** *(complete questions below)* **NO [ ]** *(go to part 5)*

Reason surgical intervention is required:

Part 5: ADVERSE EVENTS	YES	N0	Details
Blood test abnormalities?	[ ]	[ ]	
SUSARs? (Serious unexpected suspected adverse reactions)	[ ]	[ ]	

Part 6: Contact details

Name / Position of clinician completing form	Telephone number	Fax number

Final Additional Data

Patient Trial Number: …… **Patient Initials:** ……

Date of visit: ……../……../……

For ***each*** of the six outcomes below, please select the most appropriate description for the patient *at this visit:*

Item	Description	Select one (✓)
1. Headache	Absent	[ ]
	Present, stable	[ ]
	Deteriorating	[ ]
2. Tinnitus	Absent	[ ]
	Present, stable	[ ]
	Deteriorating	[ ]
3. Visual obscurations	Absent	[ ]
	Abnormal, stable	[ ]
	Deteriorating	[ ]
4. Visual Acuity	Normal	[ ]
	Abnormal, stable	[ ]
	Deteriorating	[ ]
5. Optic Disc	Normal	[ ]
	Abnormal, stable	[ ]
	Deteriorating	[ ]
6. Visual Field	Normal	[ ]
	Abnormal, stable	[ ]
	Deteriorating	[ ]

In your clinical opinion, which of the following best describes the patient's IIH at this visit? *(Please tick **one**)*

a. IIH in remission [ ]
b. Active IIH improving [ ]
c. Active IIH but stable [ ]
d. Active IIH deteriorating [ ]

APPENDIX 2

IIH Trial Questionnaires

Questionnaire 1

For each statement, please tick <u>one</u> response.

1. I feel tense and 'wound up'	(✔)
Most of the time	[ ]
A lot of the time	[ ]
Time to time, occasionally	[ ]
Not at all	[ ]

2. I feel as if I am slowed down:	(✔)
Nearly all the time	[ ]
Very often	[ ]
Sometimes	[ ]
Not at all	[ ]

3. I still enjoy the things I used to enjoy:	(✔)
Definitely as much	[ ]
Not quite so much	[ ]
Only a little	[ ]
Hardly at all	[ ]

4. I get a sort of frightened feeling like 'butterflies' in the stomach:	(✔)
Not at all	[ ]
Occasionally	[ ]
Quite often	[ ]
Very often	[ ]

5. I get a frightened sort of feeling as if something awful is about to happen:	(✔)
Very definitely and quite badly	[ ]
Yes but not too badly	[ ]
A little but it doesn't worry me	[ ]
Not at all	[ ]

6. I have lost interest in my appearance:	(✔)
Definitely	[ ]
I don't take so much care as I should	[ ]
I may not take quite as much care	[ ]
I take just as much care as ever	[ ]

7. I can laugh and see the funny side of things:	(✔)
As much as I always could	[ ]
Not quite so much now	[ ]
Definitely not so much now	[ ]
Not at all	[ ]

8. I feel restless as if I have to be on the move:	(✔)
Very much indeed	[ ]
Quite a lot	[ ]
Not very much	[ ]
Not at all	[ ]

9. Worrying thoughts go through my mind:	(✔)
A great deal of the time	[ ]
A lot of the time	[ ]
From time to time but not too often	[ ]
Only occasionally	[ ]

10. I look forward with enjoyment to things:	(✔)
As much as I ever did	[ ]
Rather less than I used to	[ ]
Definitely less than I used to	[ ]
Hardly at all	[ ]

11. I feel cheerful:	(✔)
Not at all	[ ]
Not often	[ ]
Sometimes	[ ]
Most of the time	[ ]

12. I get sudden feelings of panic:	(✔)
Very often indeed	[ ]
Quite often	[ ]
Not very often	[ ]
Not at all	[ ]

13. I can sit at ease and feel relaxed:	(✔)
Definitely	[ ]
Usually	[ ]
Not often	[ ]
Not at all	[ ]

14. I can enjoy a good book or radio or TV programme:	(✔)
Often	[ ]
Sometimes	[ ]
Not often	[ ]
Very seldom	[ ]

QUESTIONNAIRE 2:
OVERALL HEALTH

The following questions ask for your views about your health and how you feel about life in general. If you are unsure about how to answer any question, try and think about your overall health and give the best answer you can. Do not spend too much time answering, as your immediate response is likely to be the most accurate.

1. In general, would you say your health is:

*(Please tick **one** box)*

- Excellent ☐
- Very good ☐
- Good ☐
- Fair ☐
- Poor ☐

2. Compared to 3 months ago, how would you rate your health in general now?

*(Please tick **one** box)*

- Much better than 3 months ago ☐
- Somewhat better than 3 months ago ☐
- About the same ☐
- Somewhat worse now than 3 months ago ☐
- Much worse now than 3 months ago ☐

3. The following questions are about activities you might do during a typical day.

Does your health limit you in these activities? If so, how much?

	*(Please tick **one** box on each line)*	**Yes, limited a lot**	**Yes, Limited a little**	**No, not limited at all**
a)	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
b)	**Moderate activities**, such as moving a table, pushing a vacuum, bowling or playing golf	☐	☐	☐
c)	Lifting or carrying groceries	☐	☐	☐
d)	Climbing **several** flights of stairs	☐	☐	☐
e)	Climbing **one** flight of stairs	☐	☐	☐
f)	Bending, kneeling or stooping	☐	☐	☐
g)	Walking **more than a mile**	☐	☐	☐
h)	Walking **half a mile**	☐	☐	☐
i)	Walking **100 yards**	☐	☐	☐
j)	Bathing and dressing yourself	☐	☐	☐

4. During the <u>past 2 weeks</u>, how much time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	*(Please tick **one** box on each line)*	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a)	Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b)	**Accomplished less** than you would like	☐	☐	☐	☐	☐
c)	Were limited in the **kind** of work or other activities	☐	☐	☐	☐	☐
d)	Had **difficulty** performing the work or other activities (eg it took more effort)	☐	☐	☐	☐	☐

5. During the <u>past 2 weeks</u>, how much time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	*(Please tick **one** box on each line)*	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a)	Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b)	**Accomplished less** than you would like	☐	☐	☐	☐	☐
c)	Didn't do work or other activities as **carefully** as usual	☐	☐	☐	☐	☐

6. During the <u>past 2 weeks</u>, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

(*Please tick **one** box)*

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

7. How much bodily pain have you had during the <u>past 2 weeks</u>?

(*Please tick **one** box)*

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very Severe ☐

8. During the <u>past 2 weeks</u> how much did pain interfere with your normal work (including work both outside the home and housework)?

*(Please tick **one** box)*

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

9. These questions are about how you feel and how things have been with you <u>during the past 2 weeks</u>. For each question please give the one answer that comes closest to the way you have been feeling.

(*Please tick **one** box on each line)*

	How much time during <u>the last 2 weeks</u>:	**All of the time**	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
a)	Did you feel full of life?	☐	☐	☐	☐	☐	☐
b)	Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
c)	Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
d)	Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
e)	Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
f)	Have you felt downhearted and low?	☐	☐	☐	☐	☐	☐
g)	Did you feel worn out?	☐	☐	☐	☐	☐	☐
h)	Have you been a happy person?	☐	☐	☐	☐	☐	☐
i)	Did you feel tired?	☐	☐	☐	☐	☐	☐

10. During the <u>past 2 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives etc.)?

*(Please tick **one** box)*

All of the time	☐
Most of the time	☐
Some of the time	☐
A little of the time	☐
None of the time	☐

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

(*Please tick **one** box on each line)*

		Definitely true	**Mostly true**	**Not sure**	**Mostly false**	**Definitely false**
a)	I seem to get ill more easily than other people	☐	☐	☐	☐	☐
b)	I am as healthy as anybody I know	☐	☐	☐	☐	☐
c)	I expect my health to get worse	☐	☐	☐	☐	☐
d)	My health is excellent	☐	☐	☐	☐	☐

Questionnaire 3

Please answer the questions by ticking one box in each group.

Please indicate which statement best describes your own health *today.*

Mobility

- I have no problems walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual activities e.g. work, study, housework, family or leisure activities

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/ Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

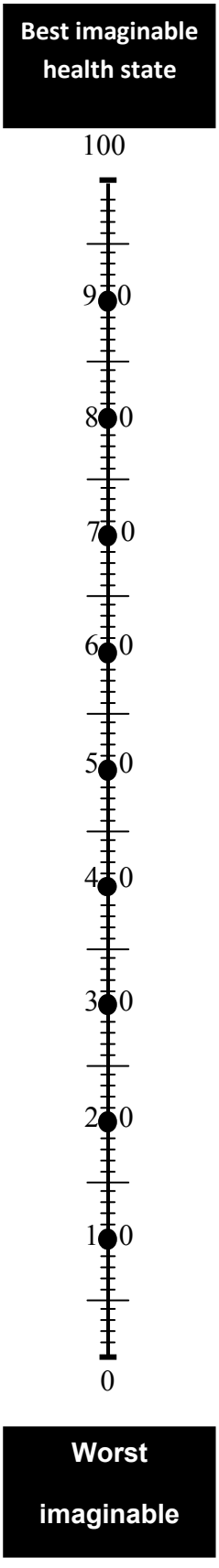
Anxiety/ Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

To help people say how good or bad their health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you could imagine is marked by 0.

We would like you to indicate on the scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box to whichever point on the scale indicates how good or bad your current health state is.

Your own health state today



APPENDIX 3

Peer-reviewed Publications and Presentations

Peer reviewed Publications

- Ball A K, Sinclair A J, Curnow S J, Tomlinson J W, Burdon M A, Walker E A, Stewart P M, Nightingale P G, Clarke C E, Rauz S. Elevated CSF leptin in idiopathic intracranial hypertension: evidence for hypothalamic leptin resistance? *Clinical Endocrinology* 2008 September; 70: 863-869

- Ball A K, Sinclair A J, Curnow S J, Tomlinson J W, Walker E A, Clarke C E, Rauz S. Cytokine profiles in idiopathic intracranial hypertension: A comparison with other neuro-ophthalmological conditions. *Investigative Ophthalmology and Visual Science* 2007 May; 48: E-abstract 926

- Ball A K, Clarke C E. Idiopathic Intracranial Hypertension (Review). *Lancet Neurology* 2006 May; 5(5):433-42.

Book Chapter

- Ball A K, Weatherby S. Idiopathic Intracranial Hypertension.
  In *Headache: A Practical Manual. Oxford University Press,* November 2008

Poster presentations at international meetings

- Ball A K, Matthews T D, Burdon M A, Jacks A S, Howman A J, Wheatley K, Lawden M, Sivaguru A, Sinclair A J, Clarke C E. 'A Randomised controlled trial of treatments for Idiopathic Intracranial Hypertension (The IIH Pilot Trial)'.
  North American Neuro-Ophthalmology Society 35th Annual Meeting, Lake Tahoe, USA, February 2009

- Ball A K, Sinclair A J, Curnow S J, Tomlinson J W, Walker E A, Stewart P M, Nightingale P G, Clarke C E, Rauz, S. 'Cytokine profiles in neurological diseases'.
  ABN and Norwegian Neurological Society Autumn Meeting, London, November 2007

- Ball A K, Sinclair A J, Curnow S J, Tomlinson J W, Clarke C E, Rauz, S. Cytokine profiles in idiopathic intracranial hypertension: a comparison with other neuro-ophthalmic conditions.
  Association of Research and Vision In Ophthalmology (ARVO) Annual Scientific Meeting, Fort Lauderdale, USA, May 2007

Platform presentations

- Ball A K, Howman A J, Wheatley K, Lawden m, Sivaguru A, Furmston A, Howell S, Sharrack B, Davies M B, Burdon M A, Matthews T D, Jacks A S, Sinclair A J, Clarke C E.
  'Randomised Controlled Trial of Treatments for Idiopathic Intracranial Hypertension (The IIH Pilot Trial)'
  Association of British Neurologists joint annual meeting with the Spanish Society of Neurology, Liverpool, June 2009

- Ball A K, Sinclair A J, Curnow S J, Rauz S
  'Idiopathic Intracranial Hypertension and Obesity'
  Neurosciences Research Forum Annual Meeting, University of Birmingham, April 2007
  (Presentation prize winner.)

- Ball A K, Clarke C E, Wheatley K
  'The Idiopathic Intracranial Hypertension Trial Pilot'
  Midlands Neurological Society Annual meeting, Birmingham, November 2005