CHILDHOOD CENTRAL NERVOUS SYSTEM ACQUIRED DEMYELINATING DISORDERS:
incidence, clinical features, MRI characteristics and prognostic features

by

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Abstract

Objectives: Acquired demyelinating syndromes (ADS) are rare childhood central nervous system disorders. In this thesis I aimed to describe the UK incidence, clinical features, MRI characteristics and prognostic features of childhood ADS.

Methods: I describe the first UK population active surveillance and one year follow up study which features multiple source ascertainment, MRI review, and blinded clinical expert panel diagnostic review. I also describe: 4 longitudinal retrospective case series delineating prognostic risk factors; outline the setup of a longitudinal cohort; and describe methodological concepts important for the design of the future clinical trials in ADS.

Results: The incidence of first onset ADS in children aged 1-15 years old was 9.83 per million children per year; the highest surveillance rate reported to date. The female-to-male ratio in children older than 10 years was 1.52:1. A trend towards higher incidence rates of ADS in children of South Asian and Black ethnicity was observed compared with White children. A number of MRI characteristics distinguished acute disseminated encephalomyelitis cases (1/3 of cohort) from clinically isolated syndrome (CIS) cases (2/3 of cohort). Of CIS cases with contrast imaging, 26% fulfilled McDonald 2010 MS diagnostic criteria. Predictive risk factors for MS diagnosis included: CIS presentation; presence of periventricular lesions on MRI brain scan; and age> 8 years.

Conclusions: The detailed study of ADS presented in this work will help to inform future clinical service delivery and clinical trial design.

Dedication

For my wonderful wife Georgiana,

    without whose unwavering love, patience and support this work would not have been

    possible;

and for my beautiful daughter Shereen,

    who brings me endless happiness and purposefulness and of whom I am very proud.

Declaration

I confirm that this work is my own and that I have been involved in the design and conduct of these studies, analysis of data and preparation of this thesis. The following aspects of these studies were undertaken as part of collaboration:

- The expert panel comprising consultant paediatric neurologists in the UK helped with case classification by consensus for the surveillance study.

- The brain and spinal cord magnetic resonance imaging scans were reviewed blinded to clinical features jointly by with one of five neuroradiologists.

- Case report forms for the surveillance study were completed with the help of UK and Ireland paediatricians, paediatric neurologists, and ophthalmologists who have completed monthly surveillance cards.

- Antibody testing and results were carried out by laboratory staff in Professor Angela Vincent's staff at the Oxford University Hospitals NHS Trust.

- Sagar Sedani helped with data collection from the England 2010 index of multiple deprivation database.

- The Neuromyelitis Optica national commissioning group identified cases for the Neuromyelitis Optica cohort study.

Acknowledgments

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ABBREVIATIONS

AAN	American Academy of Neurology
Ab	Antibody
ADEM	Acute Disseminated Encephalomyelitis
ADS	Acquired Demyelinating Syndrome
AQP4	Aquaporin-4
ARR	Annualised Relapse Rate
ASIA	American Spinal Injury Association
TM	Acute Transverse Myelitis
BBB	Blood Brain Barrier
BOSU	British Ophthalmological Surveillance Unit
BPSU	British Paediatric Surveillance Unit
CADASIL	Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
CIS	Clinically Isolated Syndrome
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CTD	Connective Tissue Disease
DIS	Dissemination In Space
DIT	Dissemination In Time
EDSS	Expanded Disability Status Scale (adult based scale).
3.0	Moderate disability in 1 or mild disability in 3-4 functional systems. No impairment of gait.
4.0	Significant disability but self-sufficient. Able to walk without aid or rest for
6.0	500m.
	Requires a walking aid - cane, crutch, etc - to walk about 100m with or without resting.
GAD	Gadolinium
IgG	Immunoglobulin
IPMSSG	International Paediatric Multiple Sclerosis Study Group
IV	Intravenous

IVIG	Intravenous Immunoglobulin
LHON	Leber Hereditary Optic Neuropathy
MELAS	Mitochondrial Encephalopathy with Lactic Acidosis
MERFF	Myoclonic Epilepsy with Ragged Red Fibers
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NHS	National Health Service
NMO	Neuromyelitis Optica
OGB	Oligoclonal Bands
ON	Optic neuritis
PLEX	Plasma Exchange
ROC	Receiving Operating Characteristic
SLE	Systemic lupus erythematosus
TM	Transverse Myelitis
TMCWG	Transverse Myelitis Consortium Working Group

CHAPTER 1: BACKGROUND

In this chapter, I will introduce the monophasic and relapsing acquired demyelinating syndromes (ADS) and their accepted definitions. I will then describe current knowledge at the time of writing on the incidence of ADS, their demographics, and clinical features. I will then examine the MRI characteristics and diagnostic criteria of paediatric onset multiple sclerosis, the most common relapsing acquired demyelinating syndrome, in relation to adult onset multiple sclerosis. I will go on discuss the immunological and investigative features in ADS. I will illustrate the current knowledge on the genetic and environmental influences on these autoimmune conditions with a focus on multiple sclerosis. I will then consider the differential diagnoses, treatments, outcomes, natural history and implications for every day functioning after ADS onset. I will conclude by highlighting the need for further studies and more detailed investigation of the incidence, clinical features, MRI characteristics and prognosis of the acquired demyelinating syndromes.

1.1 Introduction

Acquired demyelinating syndromes (ADS) are rare childhood disorders which may result in physical and cognitive disability, or ultimately be diagnosed as multiple sclerosis (MS). MS, the most common relapsing acquired demyelinating disorder in children and adults, is a chronic autoimmune inflammatory demyelinating disease of the central nervous system (CNS). MS is characterized by myelin loss, axonal degeneration and, progressive neurological dysfunction, that is usually relapsing and remitting in nature. It is often difficult to predict at ADS onset as to whether the disease will have a monophasic or relapsing course.

Multiple sclerosis is a chronic and costly neurodegenerative disease, with onset predominantly in young adulthood (late 20s- to late 40's), and is characterised by usually recurrent demyelinating inflammatory attacks to different regions of the central nervous system (brain, spinal cord) at different time points. MS is a disease with variable presentation and prognosis, and its aetiology is as yet undetermined, with current research focussing on gene-environment interactions with the immune system and MS risk (1, 2). Incidence of MS appears to be increasing worldwide with a rising female to male sex ratio (2-4) and with up to 10% of adults who develop MS having first symptoms in childhood (4-7). There is evidence that Indian and Pakistani immigrants who entered England younger than 15 years of age have a higher risk of developing MS than those that entered after this age(1). Previous MS studies have shown that adolescent females are over-represented compared to males with ratios of up to 3:1 (5-7). Adult MS studies have also shown a consistent increase in female MS incidence, compared to males, as well as a higher risk ratio of females developing CIS,(8) the first presentation of MS. Adult MS studies have also shown higher incidence and prevalence of multiple sclerosis in less deprived populations (9, 10).

Epidemiological evidence suggests early environmental exposures may influence MS risk (1, 2). Hence any epidemiological change in MS may be evident first in a paediatric population.

In children, MS is largely relapsing-remitting at onset (in more than 95%), with secondary progression and an Expanded Disability Status Score (EDSS) disability score of 6 (requires a walking aid- to walk about 100m) occurring at a median of 28 years after disease onset (11). Although there are some similarities in terms of disease presentation, especially in adolescence, differences are more apparent in younger children who more commonly present with an acute disseminated encephalomyelitis (ADEM) which may indeed be relapsing (although usually monophasic). In addition, clinical outcomes observed in childhood onset and adult onset MS share similarities; however, the severity and course differs somewhat between both groups as will be later expanded on.

1.2 Definitions of ADS and MS

The International Paediatric MS Study Group (IPMSSG), have published consensus definitions (Table 1) of paediatric acquired demyelinating disorders (ADS) and multiple sclerosis (MS) to help facilitate uniformity in clinical practice and future research (12). Encephalopathy (behavioural change or altered consciousness) distinguishes polyfocal CIS from ADEM in the definitions.

Diagnosis of MS in children, as in adults, is first heralded by onset of a clinically isolated syndrome (CIS), or more rarely acute disseminated encephalomyelitis (ADEM). Children ultimately diagnosed with relapsing-remitting MS present with an ADS followed by a second event usually within two years (12). Childhood CIS presentations with abnormal Magnetic Resonance Imaging (MRI) of the brain (i.e. more than one high T2 signal) compared to ADEM are much more likely to have relapsing disease (5, 13-21).

Recently, the new MRI McDonald 2010 MS criteria have been recommended for use in children presenting with a CIS (22), potentially allowing for MS diagnosis at first presentation of a CIS (7). There is no biomarker that differentiates between monophasic ADEM, monophasic CIS, or MS, hence a combination of clinical, cerebrospinal fluid (CSF) positive oligoclonal bands and MRI features is often used (23-25). MRI differences, in particular between ADEM and polyfocal CIS, are also not well recognised (26). The differential diagnosis of ADSs is complex and wide, especially so in childhood (27, 28) . MS (defined inTable 2) is characterized by relapses of neurological dysfunction and MRI evidence of inflammatory white matter lesions.

Table 1: Summarised IPMSSG definitions (12) for CNS Inflammatory Demyelinating Disease (2007)

Condition	Definition
Acute Disseminated Encephalo-myelitis (ADEM)	A polysymptomatic clinical event with acute/subacute onset that must include encephalopathy (behavioural change or altered consciousness). (2) MRI Brain shows multifocal (usually diffuse bilateral lesions), predominantly involving white matter. • Relapsing ADEM: symptoms or signs within 3 months of initial onset of ADEM. IF a new event occurs ≥3 months later and ≥1 month after completing steroid treatment, it is defined as: • Recurrent ADEM: recurrence of initial symptoms without involvement of new clinical areas. • Multiphasic ADEM: New event, but involving new anatomical areas of the CNS.
Clinically Isolated Syndrome (CIS)	A first acute-clinical episode of CNS symptoms which may either be monofocal or multifocal, but does not include encephalopathy (except in brainstem syndromes). The MRI will show area of white matter demyelination. These include: ***Transverse myelitis***: weakness and/or numbness of both legs +/- arms, usually with maximal deficits 1 week after symptom onset supported by demyelination on MRI spine. ***Brainstem***, ***cerebellar***, and/or ***hemispheric*** dysfunction, supported by demyelination on MRI.
Optic Neuritis (ON)	Acute or subacute loss of vision and ≥1 of: relative afferent pupillary defect (unilateral cases), visual field deficit or scotoma, impaired colour vision, optic disc oedema, or abnormal visual evoked potentials. MRI is not necessary for diagnosis.
Neuro-myelitis Optica (NMO)	Must have: i. Optic neuritis and ii. Acute myelitis iii. Must have: Spinal MRI lesion extends over three or more segments **OR** iv. NMO antibody testing is positive. The brain MRI must not meet Multiple Sclerosis diagnosis criteria

Table 2: IPMSSG Multiple Sclerosis definition

Multiple Sclerosis (MS)	- Two or more **non ADEM** episodes of CNS demyelination separated in time (4 weeks) and space. For children aged >12 years:
	- Dissemination in space can be met if: <u>MRI</u> shows three of: 1) ≥ 9 white matter lesions or 1 gadolinium enhancing lesion, 2) ≥3 periventricular lesions, 3) One juxtacortical lesion, 4) an infratentorial lesion.
	<u>OR</u> abnormal CSF (oligoclonal bands or elevated IgG index) with 2 lesions on the <u>MRI</u> (one in the brain).
	- Dissemination in time can be met if: <u>MRI</u> shows new T2 or gadolinium enhancing lesions developing ≥3 months after initial event.

1.3 Incidence

Introduction

Ideally an epidemiological study in children should: ascertain children at first onset of ADS; be a large prospective surveillance and population based study; have multi-source active case ascertainment (29); consider and if possible estimate the impact of missed cases; report clinical, demographic, and investigative features; have independent review of MRI; have expert panel case review; and utilise internationally accepted definitions (30). To date, there are no studies in children of first onset ADS or MS which fulfil all these criteria.

It cannot be assumed that the risk of relapse in children and hence the risk of developing MS is the same as in adults, and MS risk may be geographically different in children (6). There is hence an urgent need for prospective population based studies to further understand clinical, radiological, and pathobiological features as well as outcome of childhood onset acquired demyelinating syndromes.

A diagnosis of paediatric MS is currently based on consensus definitions by the International Paediatric MS Study Group (IPMSSG) (12). Current information on incidence is derived from a few studies in Europe and North America. As reported in studies of MS in adults, prevalence of paediatric MS seems to differ amongst countries, with a higher incidence reported in Northern Europe and Canada, lower in southern Europe and very low in African countries with relatively few cases reported from Japan, China or India. It is unclear whether this represents a true geographic bias, or whether the disease is under-recognized or under-reported in some areas. Two previous epidemiological surveillance studies using a single surveillance system with no MRI or post reporting verification of diagnosis by expert panel

revealed an incidence of ADS ranging from 3.7 (31) to 9.0 per million children per year (32). Furthermore, both studies predated the aforementioned consensus definitions(12).

At least 20% of children presenting with an ADS will display accepted diagnostic criteria of MS after 2 years of follow-up, suggesting an incidence of 1.8 per million children with MS. In the U.S.A a study using a large California-based database reports an incidence of ADS as 1.66 per 100,000 children per year and the incidence of paediatric MS as 0.51/100,000 (33). The median age at onset of paediatric MS in different cohorts is 11 to 12 years, with 20 to 30% being younger than 10 years, the youngest patients being less than two years.

A systematic review of the epidemiology of adult onset MS in England & Wales (34) have given a range of prevalence estimates, with average estimated at about 110 patients per 100,000 population across the adult age range. There is good international evidence of geographical variation in prevalence, best described by increasing prevalence with latitude (both north and south of the equator). This is not seen however within the data on MS in adults for England and Wales, which may be due to other causes of variation masking any trend in the limited data.

Literature search strategy

I searched the medical literature for estimates of the incidence of acquired demyelinating syndromes. I searched PubMed (Table 3) for articles published between 1st January 1980, and 1st December 2011. The search terms for the childhood central nervous system acquired demyelinating disorders were "incidence or epidemiology" and "childhood or paediatric or pediatric or children" and "demyelination or demyelinating or acute disseminated encephalomyelitis or transverse myelitis or optic neuritis or neuromyelitis or multiple sclerosis." Only original reports reporting the incidence of any or all of the ADSs were included. Review articles were not included, but their references screened for any relevant articles. For each study included, I summarised the design, incidence rates and demographic characteristics (Table 5).

Table 3: Literature search strategy for the incidence of childhood acquired demyelinating syndromes

Literature search date: 26th November 2011; Pubmed

Keywords used (using The MeSH® Database, www.ncbi.nlm.nih.gov/mesh):

Incidence; MeSH heading

Epidemiology; MeSH heading

Children; synonym for MeSH heading "child"

Paediatric; MeSH heading

Pediatric; MeSH heading

Childhood; MeSH text word

Demyelination; synonym for MeSH heading "demyelinating diseases"

Demyelinating; MeSH text word

acute disseminated encephalomyelitis; MeSH heading

transverse myelitis; MeSH heading

optic neuritis; MeSH heading

neuromyelitis; MeSH heading

multiple sclerosis; MeSH heading

Pubmed Search: *((incidence[Title/Abstract]) OR (epidemiology[Title/Abstract])) AND ((childhood[Title/Abstract]) OR (children[Title/Abstract]) OR (paediatric[Title/Abstract]) OR (pediatric[Title/Abstract])) AND ((demyelination[Title/Abstract]) OR (demyelinating[Title/Abstract]) OR (acute disseminated encephalomyelitis[Title/Abstract]) OR (transverse myelitis[Title/Abstract]) OR (optic neuritis[Title/Abstract]) OR (neuromyelitis[Title/Abstract])OR (multiple sclerosis[Title/Abstract]))*

Limits: Human, 1/1/1990- 25/11/2011

N=129 (reviews=45)

Five studies selected

Classification of evidence for diagnostic and population screening studies was described using terminology (Table 4) adapted from the American Academy of Neurology (AAN) 2011 Guideline Process Recommendations (www.aan.com/globals/axon/assets/9023.pdf accessed 29th March 2012).

Table 4: The American Academy of Neurology (AAN) 2011 Guideline Process Recommendations

Criteria for diagnostic studies:

Class I: A cohort study with prospective data collection of a broad spectrum of persons with the suspected condition, using an acceptable reference standard for case definition. The diagnostic test is objective or performed and interpreted without knowledge of the patient's clinical status. Study results allow calculation of measures of diagnostic accuracy.

Class II: A case control study of a broad spectrum of persons with the condition established by an acceptable reference standard compared to a broad spectrum of controls or a cohort study where a broad spectrum of persons with the suspected condition where the data was collected retrospectively. The diagnostic test is objective or performed and interpreted without knowledge of disease status. Study results allow calculation of measures of diagnostic accuracy.

Class III: A case control study or cohort study where either persons with the condition or controls are of a narrow spectrum. The condition is established by an acceptable reference standard. The reference standard and diagnostic test are objective or performed and interpreted by different observers. Study results allow calculation of measures of diagnostic accuracy.

Class IV: Studies not meeting Class I, II or III criteria including consensus, expert opinion or a case report.

Criteria for population Screening:

Class I
- Study of a cohort of patients at risk for the outcome from a defined geographic area (i.e., population based)
- The outcome is objective
- Also required:
a. Inclusion criteria defined
b. At least 80% of patients undergo the screening of interest

Class II
- A non–population-based nonclinical cohort (e.g., mailing list, volunteer panel) or a general medical, neurology clinic/centre without a specialized interest in the outcome. Study meets criteria a and b (see Class I)
- The outcome is objective

Class III
- A referral cohort from a centre with a potential specialized interest in the outcome

Class IV
- Did not include persons at risk for the outcome
- Did not statistically sample patients or patients specifically selected for inclusion by outcome
- Undefined or unaccepted screening procedure or outcome measure
- No measure of frequency or statistical precision calculable

Literature search Findings:

Published studies reporting on the incidence of childhood ADSs (summarised in Table 5) included one retrospective analysis of a patient database, a multicentre retrospective study, a single centre prospective study, and two prospective population based surveillance studies. The surveillance studies however predated IPMSSG consensus diagnostic definitions and did not include independent MRI and expert panel review. To date, there have been two surveillance studies studying ADSs. A Canadian surveillance study (2004-2007) estimated the incidence of childhood ADSs to be 9.0 per million (32), with 22% classified as ADEM and 78% as CIS. This study however used a single surveillance system with a card return rate of 80%; did not have MRI available or have expert panel review; included adolescents up to the age of 18; did not include neuromyelitis optica; and commenced before IPMSSG definitions were published. An earlier surveillance study from Germany (1997-1999) estimated the incidence of MS in children <16 years as 3·0 per million children, and that of ADEM as only 0.7 per year per million children (31). This study also used only one source with ascertainment from paediatric departments; did not have MRI available or expert review; and did not include other ADSs. Diagnosis of MS depends on clinical definitions and MRI criteria used. Hence, reliable ascertainment requires expert review and up to date clear definitions.

Table 5: Summary of studies investigating the incidence of first onset childhood Central Nervous System Inflammatory Demyelinating Diseases (ADSs)

Author (Year)	Study period & sample size	Study Design and setting/ AAN evidence classification	Conditions Studied	Incidence of ADS	Demographics	i. Surveillance unit used/ ii. Expert panel used	Sources of ascertainment	IPMSSG consensus definitions used	Additional / other criteria or definitions used	MRI scan review & reported	Methodology considering impact of missed cases
Langer-Gould et al(33) 2011	01/2004 – 12/2009; n= 81	Retrospective; Southern California, USA (latitudes 33-34°N). Class II	ADEM, ON, TM, other CIS, NMO	15·6 per million children ≤18 yrs/ year	56·8% female; 49% Hispanic, 19% white, 20% black; mean age= 12·6 yrs (range 0·7-18·0).	i. No ii. No	electronic database searches using ICD-9 codes, Kaiser Permanente members, medical records review.	Yes	No	No	No
Parvone et al(35) 2010	1992 – 2009; n=17	Prospective, one institution; Catania, Italy (latitudes 37-38°N). Class III	ADEM	11 per million children (<10 years)/ year	41·2% female; median age= 3·1 yrs (range 1·5- 8·0 yrs).	i. No ii. No	One paediatric neurology department	Yes (after 2007)	No	Yes 10/17	No

Author (Year)	Study period & sample size	Study Design and setting	Conditions Studied	Incidence of ADS	Demographics	i. Surveillance unit used/ ii. Expert panel used	Sources of ascertainment	PMSSG consensus definitions used	Additional / other criteria or definitions used	MRI scan review & reported	Methodology considering impact of missed cases
Toriso et al(36) 2010	09/1998 – 08/2003; n=30	Retrospective multicentre; Fukuoka, Japan (latitudes 33-34°N). Class II	ADEM, TM	7·4 per million children <15 yrs/ year	36·.7% female; mean age= 5.8 yrs (range 0-15.0).	i. No ii. No	Five major medical centres, questionnaire based.	No	Own criteria	Yes	No
Banwell et al(32) 2009	04/ 2004 – 03/2007; n=219	Prospective, surveillance; Canada (latitudes 42-80°N). Class I.	ADEM, ON, TM, other CIS.	9·0 per million children <18 yrs/ year	52·1% female; mean age= 10·5 yrs (range 0·66–18·0 years); sex ratio consistent when evaluated as a function of age.	i. One unit used (80% card return rate) ii. No	Paediatricians, paediatric neurologists and paediatric ophthalmologists	No	Own criteria likely to not have changed classification as per IPMSSG	No	No
Pohl et al(31) 2007	01/ 1997 – 12/1999; n= 28	Prospective, surveillance; Germany (latitudes 47-55°N). Class I	ADEM (n=28), MS (n=132)	0.7 per million ADEM; 3.0 per mill; MS; <16 yrs/ year	42.8% female; median age= 6.0 yrs (range 1-14 yrs).	i. One Unit used (94% card return rate) ii. No	Paediatric departments in Germany	No	No	No	No

AAN= American Academy of Neurology; ADEM = acute disseminated encephalomyelitis; BOSU = British Ophthalmological Surveillance Unit; BSPU= British Paediatric Surveillance Unit; ADS; F= female; M= male; MRI= magnetic resonance imaging; MS= multiple sclerosis; NMO = Neuromyelitis optica; ON= optic neuritis; TM= transverse myelitis; yrs= years

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1.4 Demographic & Clinical features of ADS

Multiple sclerosis in adults is most commonly a disease of individuals of white ethnicity and of Northern European ancestry (37). A recent retrospective study from the USA (Kaiser Permanente members, medical records review) showed the incidence of childhood ADSs and MS to be higher in black children compared with white and Hispanic children (33). A Japanese retrospective multicenter study showed the male to female ratio of ADEM to be 2.3:1, and that ADEM was three times more common than MS (36). These observations regarding the demographics of childhood ADSs support the hypothesis that environmental influences (which might include vitamin D) may indeed be acting as early as in childhood.

The first attack of demyelination is characterized by a constellation of neurological deficits (Table 6), occasionally accompanied by systemic features, with acute or subacute onset in a previously healthy child. In one large cohort study of childhood ADS, long-tract signs (motor, sensory, or sphincter dysfunction) was the most common finding (76%), followed by symptoms localised to the brainstem (41%), optic neuritis (22%), and transverse myelitis (14%). Monofocal presentation was more common in adolescents. CISs are more common than ADEM in children. CIS is a clinically heterogeneous entity and has a higher incidence of subsequent MS diagnosis than ADEM. CIS can be monofocal affecting a localised part of the CNS (optic neuritis, transverse myelitis, brainstem syndrome, hemispheric syndrome) or multifocal, affecting multiple parts of the CNS but must not include encephalopathy. A high index of suspicion for ADS is required in children presenting with neurological deficits, encephalopathy, and first onset status epilepticus.

In this next section I will discuss the demographic, clinical, and neuroimaging features of the monophasic and relapsing ADS phenotypes.

Table 6: Presenting symptoms and signs in CNS inflammatory demyelination

- Bilateral visual loss (involvement of both eyes within 30 days of each other
- Unilateral visual loss (one eye only)
- Double vision
- Intranuclear ophthalmoplegia
- Facial pain and numbness
- Loss of sensation (one side of face)
- Weakness (one side of face only)
- Other brainstem signs
- Loss of sensation (one sided, involving face, arm and leg)
- Weakness (arm and leg ± face, all on same side of body)
- Loss of sensation (both legs and/or both arms at the same time)
- Weakness (both legs and/or both arms)
- Sphincter disturbance (bladder retention ± bowel dysfunction)
- Loss of balance (gait ataxia)
- Impaired co-ordination of arms/legs (limb ataxia)
- Confusion or impaired alertness (encephalopathy)
- Fever
- Neck stiffness
- Headache
- Seizures
- Vertigo
- Fatigue
- L'Hermitte's symptom (electrical sensation down the back produced by bending the neck forward).

1.4.1. Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is defined as an episode of inflammatory central nervous system (CNS) demyelination with acute/subacute onset, polyfocal neurological deficits accompanied by encephalopathy (behavioural change or altered consciousness)(12). There is often a wide variation in the severity of the illness. Occasionally, ADEM can present as a subtle disease, with nonspecific irritability, headache and somnolence. However, ADEM can present with a rapid progression of symptoms and signs to coma and decerebrate rigidity requiring admission to the Paediatric Intensive Care Unit (PICU), and may result in death (18). The recent International definitions (see Table 1) emphasises that encephalopathy must be present for the term 'ADEM' to be used in a child with acute demyelination accompanied by multifocal MRI lesions. In the absence of clear evidence of an infectious cause, the MRI findings should define the distribution of the CNS demyelinating inflammatory process. Brain MRI changes in ADEM are supportive but not diagnostic and often reveal multifocal, diffuse and hyperintense T2 white matter lesions. The grey matter (especially basal ganglia and thalamus) is frequently involved, and the spinal cord MRI may also show intramedullary lesions (Figure 1). The MRI brain changes in ADEM however have not been well characterised and as such further studies are required to better understand the MRI changes in ADEM compared to polyfocal clinically isolated syndromes.

ADEM is more common in children than adults, although there are no adult epidemiological studies. Available population based incidence data of ADEM in childhood have reported an incidence of 0.7–4 per million children/year (31, 32, 38). ADEM occurs more commonly in young children less than 10 years of age (equal male: female ratio). ADEM may be preceded

by infectious symptoms, although a specific pathogen is rarely implicated. Meningism, fever, and seizures are more commonly seen in ADEM as compared to clinically isolated syndromes. Outcome after ADEM is often good with a complete recovery expected in approximately 70% within a few weeks. However, ADEM may result in varying levels of neurodisability (physical, cognitive, neuropsychiatric) or very rarely death (18, 39).

ADEM is classically described as an acute, monophasic illness. Prospective studies internationally are underway to establish more detailed outcome measures in this group of patients. New deficits within 3 months of onset are currently considered to be part of the same acute episode. Further ADEM episodes occur rarely and happen in two main situations: recurrent ADEM and multiphasic ADEM (Table 1). In up to 20% of patients ADEM may also be the first attack of MS. The diagnosis of MS should be considered in cases of recurrent demyelination.

Figure 1: MRI brain changes in a child with ADEM demonstrating diffuse bilateral white matter, cerebellar, basal ganglia lesions and a spinal lesion.
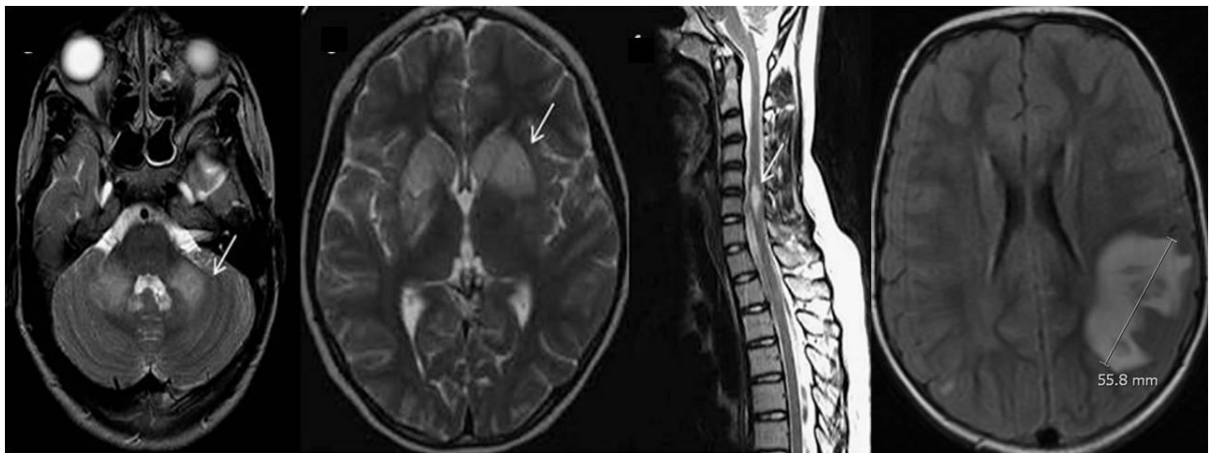
1.4.2 Clinically Isolated Syndromes

A clinically isolated syndrome (CIS) is a first acute-clinical episode of CNS symptoms (Table 6) which may either be monofocal or polyfocal (Table 1), but does not include encephalopathy (except in brainstem syndromes). The MRI shows areas of inflammatory demyelination which may be symptomatic or silent.

A Clinically Isolated Syndrome is a clinically diverse entity with a higher risk of subsequent MS diagnosis than ADEM (5, 40). Clinically Isolated Syndrome have recently been usefully classified into 5 different types to aid clarity in phenotypic descriptions (27):

Type 1 CIS: clinically monofocal, at least one asymptomatic MRI lesion

Type 2 CIS: clinically multifocal, at least one asymptomatic MRI lesion

Type 3 CIS: clinically monofocal, MRI may appear normal; no asymptomatic MRI lesions

Type 4 CIS: clinically multifocal, MRI may appear normal; no asymptomatic MRI lesions

Type 5 CIS: no clinical presentation to suggest demyelinating disease, but MRI is suggestive.

Examples of monofocal syndromes include:

- Transverse myelitis

- Optic neuritis; unilateral or bilateral.

- Brainstem, cerebellar, or hemispheric dysfunction.

In this next segment, I will describe the two most common childhood syndromes, transverse myelitis and optic neuritis (subject to a more detailed study and review in Chapter 3.1).

Childhood transverse myelitis (TM) is an inflammatory disorder of the spine (41). It is a potentially devastating condition with variable outcome (42). TM has been more commonly reported in adults, but occurs in children in approximately 20% of all cases (43). The majority of published studies on TM are retrospective case series reviews. Two prospective TM surveillance paediatric studies in Canada (32) and UK neurology centres (44) showed the incidence of TM to be 2 per million and 1.7 per million children respectively. In recent literature (2007-2010), there is a trend that male children were more likely to present with TM with ratios of 1.04-1.6:1 reported (32, 43-46). There appears to be a bimodal distribution with children predominantly affected under 5 years and older than 10 years of age (43, 44). In the Canadian and UK population studies, mean ages were 11.0 years (range 0.66–17.35) and median 9 years (0.5-15.9) respectively. The adult literature has also reported another peak between 30-39 years of age (47). Idiopathic TM represents approximately 14-22% of all first CNS Inflammatory Demyelination syndromes (15, 32) and there appears to be no seasonal influence, or difference in ethnicity prevalence.

Definitions of TM

Although reports of TM date back to 1882 (48, 49) there has been a recent effort in classifying and defining TM in order to facilitate biomarker discovery and clinical trials. In 2002 the Transverse Myelitis Consortium Working Group (TMCWG) published criteria for idiopathic TM (41). These criteria have to include all of the following:

1. Development of sensory, motor, or autonomic dysfunction attributable to the spinal cord.

2. Bilateral signs and/or symptoms (though not necessarily symmetric).

3. Clearly defined sensory level.

4. Inflammation within the spinal cord demonstrated by CSF pleocytosis or elevated IgG index or gadolinium enhancement.

5. If none of the inflammatory criteria are met at symptom onset, repeat MRI and lumbar puncture evaluation between days 2 and 7 following symptom onset may be used to meet criteria.

6. Progression to nadir between 4 hours and 21 days following the onset of symptoms (if patient awakens with symptoms, symptoms must become more pronounced from point of awakening).

7. (i) Exclusion of extra-axial compressive aetiology by neuroimaging (MRI; CT of spine not adequate).

   (ii) Other presentations to be excluded:

   - History of previous radiation to the spine within the last 10 years

   - Clear arterial distribution clinical deficit consistent with thrombosis of the anterior spinal artery

   - Abnormal flow voids on the surface of the spinal cord consistent with arterio-venous malformation.

In 2007, The International Paediatric MS Study Group (IPMSSG) classified TM as in adult literature as a subtype of clinically isolated syndrome (CIS) (12). Since the publication of the TM criteria (41), seven paediatric case series (Table 7) have been published with a total of 190 cases. Five studies are retrospective, and hence subject to confounding factors and selection bias to the more severe cases. Two studies were prospective in nature and

included ascertainment from neurology centres only (where milder cases may not be seen) with relatively short follow up. None of the studies used similar criteria, investigative procedures, or outcome measures at the outset. There is hence a need for standardising core outcome measurement, and for prospective longitudinal large population based study designs. Nevertheless, data derived from these studies are informative and reviewed in the subsequent sections.

Clinical Features of TM

The clinical features of TM depend on the location and extent of the spinal cord lesion. The spinal cord dysfunction presents with motor (weakness of the limbs), sensory, and sphincter disturbance which may be asymmetric with varied presentation and severity. Clinically, neurological signs are caused by interruption of neuroanatomical pathways in the transverse plane of the cord, and a resulting sensory level is also characteristic (50). MRI lesions do not always result in a corresponding clinical sensory level (45). When myelitis also occurs in the context of encephalopathy, and polyfocal neurological symptoms with inflammatory demyelinating lesions in the brain, Acute Disseminated Encephalomyelitis (ADEM) is diagnosed. The differential diagnosis is wide, and in Figure 2, I devise an algorithm on how to approach non-compressive myelopathy presentation. Table 7 summarises the recent case series in children with TM highlighting the cardinal clinical features. Most children reach a nadir within the first 1-2 weeks of presentation (most common symptoms being pain, lower limb weakness and bladder dysfunction). In the majority of children a sensory level was detectable (75-95%). More than half of patients have a thoracic clinical sensory level, and the rest have a cervical or lumbosacral level. A 'plateau' typically lasts for approximately one

week before ongoing recovery begins. The recovery period may extend to several years after the initial insult. Motor deficits tend to recover before bladder dysfunction.

In adults the American Spinal Injury Association (ASIA) scale of myelopathy, rates patients according to severity:

A = Complete: No motor or sensory function is preserved in the sacral segments S4-S5

B = Incomplete: Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.

C = Incomplete: Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.

D = Incomplete: Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.

E = Normal: Motor and sensory function are normal.

Table 7*:* Summary of recent largest case series of clinical features for TM in children (43-46, 51-53)

Ref	Alper 2010	DeGoede 2010	Kalra 2009	Yiu 2008	DaJusta 2008	Pidcock 2007	Defresne 2003
Setting, Design & Follow up	USA, Pittsburgh; 1 centre retrospective MRI study review; 1985-2008; 5.2yrs mean follow up 0.04-13.1)	UK, 14 regional Paediatric Neurology centres; Prospective surveillance ; 2002-2004; 0.5 yr follow up	India; prospective Case-control One centre 2003-2007 1 yr follow up	Australia; 1 centre retrospective comparison to ADEM 1997-2004 1.0 yr median follow up (0.3-8.5 yrs)	USA; New Jersey; Retrospective review 1995-2004 Mean follow up 2.3 yrs	USA, Baltimore; 1 centre retrospective review-idiopathic TM; 2000–2004 3.2 yr median follow up	France; retrospective review; single centre 1965–1995 6.5 yr median follow up (1-20 yrs)
Demo-graphics	27 cases; Mean age 9.5yrs yrs (0.5-16.9); M:F= 1.07	41 cases ; Median age 9yrs (0.5-15.9); M:F= 1.56	15 cases; Mean age 7.9 yrs (3.5-14 yrs). M: F= 1.5:1.	22 cases; Median age 7.5 yrs (0.3-15 yrs) M:F= 1.6:1	14 cases; Mean age 11.2yrs (0.7-18) M:F= 1.3:1	47 cases; Mean age 8.3 yrs, clustering 0-3, 5-17 yrs M:F = 1.04	24 cases; Mean age=8 (2-14) M:F= 0.85
TMCWG Criteria used/ exclusions	Yes ; 14 definite TM, and 13 probable 2 excluded with NMO none MS	No- All probable TM except 2: vascular myelopathy. No relapse at 6 months	No- but all probable TM;	Yes Excluded: 1NMO, 1 CTD, 1 radiation myelitis	Yes	Yes 2 had recurrent TM, 1 NMO, 1 MS, 1 ADEM	No- but all probable TM None developed MS;

Ref	Alper 2010	DeGoede 2010	Kalra 2009	Yiu 2008	DaJusta 2008	Pidcock 2007	Defresne 2003
Clinical features	4 monoparesis, 20 paraparesis, 3 tetraparesis	27 sensory (22 with level), 34 motor (15 flaccid legs, 13 arms + legs involved), 26 sphincter; 6 cerebral involvement; 1 had ON + TM.	Mean time to nadir 3.9 days (0.5-14 days). 2 required mechanical ventilation. Motor improved before sphincter. At 3 months, 8 ambulatory (4 with support)	weakness limbs-lower 100%, upper 41% 68% Bladder disturbance 55% Sensory 64% Pain	All lower limb motor deficits & bladder dysfunction Sensory; 35% cervical, 65% thoracic	At nadir (mean 2 days): 89% couldn't walk ± ventilated; 85% sphincter dysfunction; sensory level cervical 25%, thoracic 53%, lumbar 5%, sacral 3% (1/36), unclear in 14%	Nadir of 5 days. Pain (88%), motor loss (1/2 bilateral, lower limbs ± upper) preceded sphincter dysfunction (15/24) 12% cervical, 88% thoracic.
Treatment	n/a	30/36 high dose steroids	All received high dose IV steroids for 5 days	21/22 High dose IV steroids mean 5 days & tapering oral prednisolone 4 weeks	All high dose IV steroids ± IVIG	70 % IV steroids 33%, IVIG 15% PLEX	High dose steroids, 6 not received treatment
Outcome/ disability	n/a	80% started recovery<2 weeks; 19 complete /8 good/ 3 fair /6 poor*; 17 had continuing bladder problems	8 full recovery, 3 non-ambulatory, 7 Bladder disturbances. *1 deaths	61% complete /21% good/ 6% fair /6% poor1 Bladder dysfunction (14% moderate/ severe)	4/14 full motor & bladder recovery 4/14 non-ambulant bound & Intermittent catheterisation (cervical levels)	At median 3.2 yrs: 43% were unable to walk 30 feet and 21% required a walker or other support, 50% required bladder catheterisation *2 deaths	2/16 (13%) children had severe motor sequelae 5/15 had severe sphincter dysfunction *1 death

*: Normal= complete recovery; good= insignificant sequelae; fair= sequelae but not interfering with daily life; poor= sequelae interfering with daily life.

TM= acute transverse myelitis ADEM= Acute Disseminated Encephalomyelitis; CTD= connective tissue disease; IV= steroids; IVIG= Intravenous immunoglobulin; M: F= male to female; MS= multiple sclerosis; NMO= Neuromyelitis Optica; ON= optic neuritis; PLEX= plasmapharesis; yr= year

Figure 2: Algorithm for non-compressive transverse myelopathy (non trauma/ tumour)

- Confirm myelopathy; symptoms, signs, and time course
- Elicit on history and examination features suggestive of: infection; systemic inflammatory disease; CNS inflammatory demyelination; vascular/ischemia; trauma; exposure to radiation; tumour

- MRI spine and brain with Gadolinium contrast

- Non- compressive myelopathy: Lumbar puncture for CSF pleocytosis or raised IgG index

- Compressive myelopathy (e.g. tumour, haematoma): Appropriate management (see chapters XX)

Serologic or clinical evidence of systemic inflammatory/ connective tissue disease:
SLE,
 sarcoidosis,
 Behcet's disease,
 Sjogren's syndrome,
 mixed connective tissue disorder

CNS manifestations of infection:
Mycoplasma pneumonia,
Lyme disease,
Tuberculosis
viral infection (e.g. HTLV-1; HIV; HSV; enteroviruses; VZV; EBV; CMV; HHV).

CNS Inflammatory Demyelination:
- Brain MRI abnormalities meeting MS diagnostic criteria for dissemination in space
- Presentation (polyfocal neurological deficits and encephalopathy) and MRI findings consistent with ADEM.
- Criteria for NMO diagnosis met

Non Inflammatory causes:
- Spinal cord ischaemia/ vascular
- Radiation myelitis
- Neurodegenerative disorders (e.g. X linked adrenoleukodystrophy, Krabbe disease, HSP)
- Metabolic/nutritional deficiencies (e.g. Arginase, Vitamin B12, Folate, Copper, biotidinase, and abetalipoproteinaemia and Vitamin E deficiencies)

Idiopathic Acute Transverse Myelitis (TMCWG criteria)

CMV: cytomegalovirus; CNS: Central Nervous System; EBV: Epstein–Barr virus; HIV: human immunodeficiency virus; HSV: herpes simplex virus; HHV: HSP; Hereditary spastic paraplegias; human herpes virus; HTLV-1: human T-cell lymphotropic virus-1; IgG: Immunoglobulin G; MRI: Magnetic Resonance Imaging; NMO: neuromyelitis optica; SLE: Systemic lupus erythematosus; TMCWG: Transverse Myelitis Consortium Working Group; VZV: varicella zoster virus;

Optic Neuritis

Childhood optic neuritis (ON) due to demyelination is one of the most common CIS events in children, and is a potentially treatable condition that may lead to visual impairment. Optic neuritis is clinically defined as: Acute or subacute loss of vision and ≥1 of: relative afferent pupillary defect (unilateral cases), visual field deficit or scotoma, impaired colour vision, optic disc oedema, or abnormal visual evoked potentials. MRI is not necessary for diagnosis (see Table 1).

A recent Canadian surveillance study showed an incidence of 0.2 per 100,000 children (32). However, incidence rates are likely to be geographically different and more studies are needed. Isolated ON may also be the first manifestation of Multiple Sclerosis (MS) or Neuromyelitis Optica (NMO). The natural history of childhood optic neuritis (ON) remains relatively unreported. Case series reported in the literature have tended to be single centre studies, not included NMO as an outcome and some have included cases of polysymptomatic clinically isolated syndromes (CIS) at presentation (54-59).

Bilateral optic neuritis is more common in children than adults (approximately half of childhood optic neuritis is bilateral). Despite severe acute visual loss, approximately 70-80% of children will recover visual acuity (snellen of 6/9 or better). Both unilateral and bilateral optic neuritis can be the first manifestations of MS or Neuromyelitis Optica. In recent studies of children with optic neuritis , 20-45% experienced further demyelinating attacks leading to a diagnosis of MS after follow-up periods of approximately two years. Recurrent optic neuritis and the presence of MRI brain lesions extrinsic to the optic nerves has been associated with an increased likelihood of MS after ON onset.

1.4.3　Neuromyelitis Optica (NMO)

Neuromyelitis Optica (NMO) is a severe immune mediated inflammatory demyelinating condition characterised by the presence of both optic neuritis and transverse myelitis occurring simultaneously or separated in time and distinct from multiple sclerosis. Neuromyelitis optica (NMO) is also characterised by the presence of the NMO-IgG antibody directed against the astrocytic water channel protein Aquaporin-4 (60); and this discovery has broadened the disease spectrum. NMO-IgG appears to be a specific test as it is invariably negative in paediatric MS (61, 62). NMO may initially present as an isolated optic neuritis (with abnormal visual evoked potentials) in adults (63) and also in childhood (64) or as TM before further relapses reveal the underlying diagnosis (63). It can be a monophasic illness but is usually a relapsing remitting disorder in the paediatric population. NMO is a very rare disorder comprising 3-8% of the childhood Acquired demyelinating syndromes (61). LETM is a feature of NMO but can also occur in monophasic TM and paediatric multiple sclerosis (43, 61, 65).

In 2007, The International Paediatric MS Study Group (IPMSSG) defined NMO as having all of the following criteria:

1- Optic neuritis and acute myelitis.

2- Either a spinal MRI lesion extending over three or more segments or be NMO positive on antibody testing.

Two recent adult diagnostic criteria were developed on the basis of the most recent clinical, MRI and AQP4 antibody results:

A. Revised diagnostic criteria (66); two absolute criteria:

(i) optic neuritis, (ii) myelitis.

And at least two of three supportive criteria:

(i) Spinal cord MRI lesion extending >2 vertebral segments,

(ii) MRI criteria not satisfying the revised McDonald diagnostic criteria (67) for MS,

(iii) AQP4 antibody in serum.

B. The National MS Society task force on differential diagnosis of MS, (27); major criteria (all are required, but may be separated by an unspecified interval):

(i) Optic neuritis in one or two eyes

(ii) Transverse myelitis, clinically complete or incomplete, but associated with MRI evidence of spinal cord lesion extending >2 spinal segments on T2-weighted MRI images and hypointensities on T1-weighted images when obtained during acute episode of myelitis, and

(iii) no evidence for sarcoidosis, vasculitis, clinically manifest systemic lupus erythematosus (SLE) or Sjogrens syndrome (SS), or other explanation of the syndrome.

Minor criteria, from which at least one must be fulfilled:

1. Most recent brain MRI scan of the head must be normal or may show abnormalities not fulfilling the Barkhof criteria used for McDonald diagnostic criteria including:

(i) Non-specific brain T2-signal abnormalities not satisfying the Barkhof criteria for dissemination in space used in the revised McDonald criteria,

(ii) lesions in the dorsal medulla, either in contiguity or not in contiguity with a spinal cord lesion,

(iii) hypothalamic and/or brainstem lesions,

(iv) linear periventricular/corpus callosum signal abnormality, but not ovoid, not extending into the parenchyma of the cerebral hemispheres in Dawson finger configuration.

2. Positive test in serum or CSF for NMO-IgG/aquaporin-4 antibodies

Table 8 summarises the clinical features in the three recent case series of paediatric NMO using diagnostic criteria. Although the current diagnostic criteria are as recommended by the IPMSSG, it is likely that modifications need to be considered with evolution of new evolving MRI criteria such as in Miller et al., 2008. Further prospective studies are needed to clarify the spectrum of these diseases.

Table 8: Summary of recently described paediatric NMO case series (61, 68, 69)

Ref	Setting, Design & Criteria Used	Demo-graphics	NMO-IgG & CSF OGB	First attack & course/ Time to first relapse/ Annualised relapse rate (ARR)	MRI Brain features	Disease Modifying Treatment	Outcome/ disability
Collongues 2010	Multicentre (mainly adult); retrospective; France; Follow up mean 19.3 yrs; Wingerchuk 2006 criteria	12 cases Age: 14.5 yrs median (4.1-17.9) 3F:1M	8/12 NMO-IgG positive	First attack: 6ON/5SC/1OS All relapsing-remitting; first attack interval 17 months (7–154)	6/12 MRI brain abnormal (1-10 lesions) 3 MS radiological criteria positive (2MS/1ADEM) 0 Barkhof	All treatments used: Azathioprine; cyclophosphamide; glatiramer acetate; IVIG; interferon; mitoxantrone; MMF; rituximab	Median time to EDSS 4= 20.7 yrs Vision: residual visual loss +1 logMAR or 20/200 Snellen=1.3 yrs.
Lotze 2008	Retrospective single centre; USA; Follow up 4 yrs median (0.6-9); Wingerchuk 2006 criteria	9 cases Age: 14yrs median (1.9-16); All female	6/9 NMO-IgG positive (1 had recurrent TM only)	First attack: 5 OS/1TM/2ON All relapsing ARR=2.6	9/9 MRI brain abnormal (5 symptomatic)	All treatments used: 6 steroids + MMF 5 rituximab 1 monthly IVIG 1had azathioprine, glatiramer, and monthly PLEX.	Median EDSS=3 (range 0-8)
Banwell 2008	Selected prospective cohort; Canada & Argentina; Follow up 36 months median (1.2-126 months); Wingerchuk 1999	17 cases Age: 10.4 yrs median (4.4–15.2) 3.2F:1M	8/17 NMO-IgG positive 13 CSG OGB negative (1 recurrent ON, and 1 recurrent TM NMO-IgG positive; 68 other CNS inflammatory demyelination were negative)	9 relapsing (NMO-IgG pos) 8 monophasic (NMO-IgG pos)	9/17 MRI brain abnormal	At time of serum: 7 prednisone, 1 glatiramer acetate, 1 interferon-1a, 2 monthly IV cyclophosphamide	1 non-ambulant, 1 gait limited aid not required; Vision: 12/18 decreased visual acuity or severe visual impairment (4/18)

ADEM= Acute Disseminated Encephalomyelitis; ARR= annualised relapse rate; EDSS= Expanded Disability Status Scale; IVIG= intravenous immunoglobulin; MMF= mycophenolate mofetil; MRI= Magnetic Resonance Imaging; MS= Multiple Sclerosis; NMO-IgG= Neuromyelitis Optica antibodies; ON= Optic Neuritis; OS= Optico-spinal; PLEX= plasmapharesis; SC= Spinal Cord; yrs= Years

Paediatric NMO-spectrum disorders

Cases which are NMO-IgG positive but not fulfilling current criteria have been described as NMO spectrum disorders in the literature, and the spectrum of these disorders is expanding both in adults and also in childhood (70).

The largest series on paediatric NMO spectrum disorders involved a cross-sectional study from one lab (USA), where 88 consecutive NMO-IgG seropositive paediatric patients were ascertained and followed up for a median of one year (71). Clinical information was available for 58 (66%) children with 88% being girls and nearly three-quarters non-white, hence highlighting the female predominance and ethnic variation. The median age at symptom onset was 12 years (range 4–18). Presenting symptoms involved the brain in 9 patients (16%). Median duration between attacks was 3 months (range 1– 87 months). All but one (98%) had at least one attack of optic neuritis (78%) or transverse myelitis (78%). Other attack-related symptoms involved the brain or brainstem in 26 patients (45%). Thirty-eight (66%) cases fulfilled NMO diagnostic criteria (66) at follow up. The median longitudinal extent of attack-related spinal cord MRI abnormalities was 10 vertebral segments. Thirty-eight (68%) had brain MRI abnormalities, predominantly involving periventricular areas and (in descending order of frequency) -the medulla, supratentorial and infratentorial white matter, midbrain, cerebellum, thalamus, and hypothalamus. Surprisingly, additional autoantibodies were detected in 57/75 patients (76%), and 16/ 38 (42%) had a coexisting autoimmune disorder recorded (SLE, Sjogren syndrome, juvenile rheumatoid arthritis, Graves disease). Although this study provides useful information, conclusions cannot be universally extrapolated given the many limitations including that the lack of information on a third of patients (possibly because of a milder course), the relatively short follow up period, and the referral centre-based retrospective lab ascertainment.

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MRI brain abnormalities in NMO

In children in particular the presence of brain lesions should not exclude NMO as a diagnosis as lesion located in the hypothalamus, brainstem, or cerebral white matter, have been described in children who have typical features of NMO (as defined in Wingerchuk et al., 2006) (Figure 3). Brain lesions in paediatric NMO hence appear to occur more commonly (50-100%) when compared with adult NMO (25%) (63). A recent case series (69) showed that the first brain MRI in paediatric NMO (as defined in Wingerchuk et al., 2006) can show a diffuse inflammatory process, such as MS-like (2 patients) or acute disseminated encephalomyelitis-like lesions (1 patient). Brain lesions in another series (68) also confirm this observation and demonstrated that MRI brain changes in paediatric NMO frequently involve the diencephalon. In another series (61) 9/17 children with NMO (Wingerchuk et al., 2006) had brain lesions. It is important to recognise the spectrum of brain abnormalities in NMO as the occurrence of such lesions and sometimes the presence of encephalopathy and polyfocal neurological deficits may resemble ADEM, with misleading implications as to prognosis and therapy.

Figure 3: MRI brain FLAIR sequences in a five year old child with relapsing NMO showing from left to right multiple large, diffuse juxtacortical and deep white matter lesions. There is also a left internal capsule lesion with restricted diffusion. This relapse was characterised by acute onset encephalopathy and right sided hemiplegia. The case was treated with plasma exchange and on recovery was ambulatory with mild residual motor deficits. The patient has severe visual impairment from previous attacks of optic neuritis with onset at 3 years of age and persistently high NMO-IgG levels.
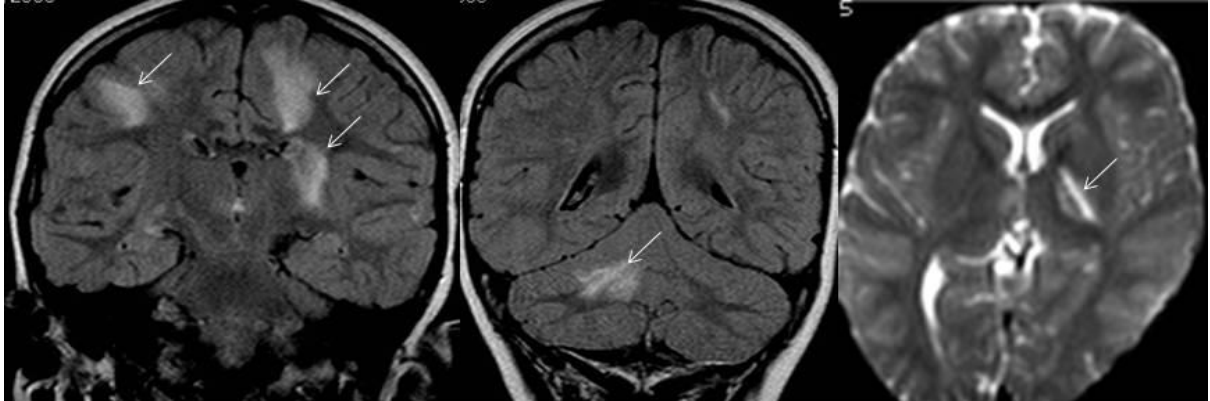
1.4.4 Multiple sclerosis: children compared to adults

Multiple sclerosis (MS) is a disabling and chronic neurodegenerative central nervous system inflammatory demyelinating disease (ADS), affecting cognition, motor abilities, and quality of life. It is characterized by progressive neurological dysfunction and multiple symptoms, which are difficult to manage(72). Diagnosis of MS in children, as in adults(40), is first heralded by onset of a clinically isolated syndrome (CIS) such as optic neuritis, or more rarely acute disseminated encephalomyelitis (ADEM) (13, 15, 20, 21, 23). Recently, the new MRI McDonald 2010 MS criteria have been recommended for use in children presenting with a CIS(22), potentially allowing for MS diagnosis at first presentation of a CIS(7). There is as yet no biomarker that accurately differentiates between ADEM, monophasic CIS, or MS (23, 25).

Clinical Presentation of MS in children compared to adults

The International Paediatric Multiple Sclerosis Study Group (IPMSSG) have published consensus definitions for paediatric acquired demyelinating disorders (ADS[s]) and MS to facilitate uniformity in clinical practice and epidemiological research (12). This definition states that children ultimately diagnosed with relapsing-remitting MS present with an ADS followed by a second event usually within two years (12). Childhood CIS presentations with an abnormal Magnetic Resonance Imaging (MRI) of the brain (i.e. more than one high T2 signal) compared to ADEM are much more likely to have relapsing disease (13, 15, 20, 21, 23). Recently, the new MRI McDonald 2010 MS criteria have been recommended for use in children presenting with a CIS (22), hence potentially allowing for MS diagnosis at first presentation of a CIS (7). There is no biomarker that differentiates between monophasic ADEM, monophasic CIS, or MS, hence a combination of clinical, cerebrospinal fluid (CSF)

positive oligoclonal bands and MRI features is suggested to support clinician decision making (23, 25).

There is general consensus that MS in adolescents is probably similar to that in adults both in terms of both underlying pathophysiology and evolution. The slower onset of progression to irreversible disability in younger patients compared to older adults may be attributable to the fact that onset of the disease is closer to the true biological onset compared to adult onset disease who may indeed have an apparently clinically silent phase with brain white matter lesions. It is likely that the biological processes are hence indeed the same but with variation in the initial clinical phase (symptomatic vs silent) of the disease hence suggesting a continuum (73, 74). There are most likely more differences between MS in younger children and adults. In a study analysing cerebrospinal fluid response in children with very early onset MS (n =4-; mean age= 7.2 years ± 2.7) compared to later onset (mean 15.1 years ± 1.7 years)- fewer patients had an elevated IgG index suggesting a more immature immune response. In an MRI brain study by the same group 13 children with early onset MS (median age 8.9 years) compared to 18 with late onset MS (median age 14.47 years, range [11.78-18.00], 61% girls) had: fewer well-defined ovoid T2-bright lesions; and more often had confluent lesions on their first MRI (also 92% vs 29% had a reduction in the number of T2-bright lesions on a subsequent scan). These observations add weight to the fact that younger patients with ADS and MS may have differences with regards biological processes and clinical progression (75, 76).

Difficulty occurs in children compared to adults, as the first onset of an inflammatory demyelinating event may be an acute disseminated encephalomyelitis in approximately 1/3 of patients. In adults, ADEM is a very rare presentation. ADEM is likely to have a monophasic

course, compared to CIS presentations with abnormal MRI scans. Studies in both children and adult have shown that it often difficult to distinguish between ADEM, polyfocal CIS and MS (25, 77-79). ADEM, polyfocal CIS and MS MRI changes often overlap, and children with MS have been reported to present with encephalopathy. In addition the term encephalopathy is loosely defined and often difficult to apply consistently amongst cohorts (20). In Chapter 2.5 I describe a study which describes the MRI differences between ADEM and CIS with abnormal MRI scans.

The majority of childhood MS has a relapsing remitting onset at initial progress (more than 95%), whilst approximately 15% of adult onset MS has been described as primary progressive (Figure 4) at onset (5, 37).

Figure 4: Usually course of multiple sclerosis in childhood
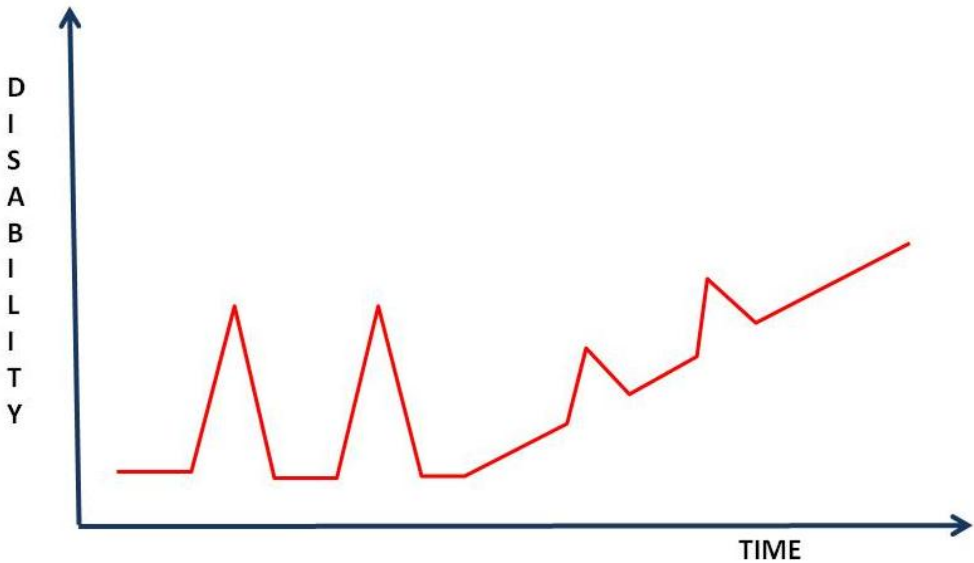
MS Relapse rates

Studies following children within the first 2-5 years of disease onset have shown a higher frequency of clinical relapses (80) (annualized relapse rate [ARR] 0.9-1.1) (Table 9) compared to adults, as opposed to those with longer follow-up times (ARR 0.5-1). In adults, relapse frequency in the first two years after onset appears to have some association with long term outcome and disability (81). Despite this adult participants in the trials of interferon and glatiramer acetate and the recent new oral drug therapies, already had disease duration of several years. There have been no paediatric studies as yet examining early relapse rates and correlation with longer term neurodisability outcome.

Table 9: Annualized relapse rates (ARR) in paediatric MS (not including first attack)

Study	Study duration	Study type	Sample Size	ARR
(82) Ghezzi 2002	First 2 years	Prospective cohort 5 centres	n=54	1.3
(11) Renoux 2007	First 2 years	Data from database registry from 13 adult centres	n=394	1.9
(80) Gorman 2009	First 3.7 years	Single centre; prospective follow up	n=21	1.1
(82) Ghezzi 2002	First 5 years	Prospective cohort 5 centres	n=54	1.0
(83) Boiko A 2002	16.3 years	Single centre database registry	n=116	0.54
(84) Deryck 2006	28.7 years	Single centre retrospective study	N=49	0.47

Diagnosis of paediatric MS compared to adult MS

The diagnosis of paediatric MS, like adult MS, has relied on clinical and supportive MRI criteria showing lesion dissemination in time (DIT) and dissemination in space (DIS), after exclusion of alternative causes. Adult MRI criteria, since their first introduction (McDonald 2001) have continually continued to be redefined with the introduction of the McDonald 2005 and 2010 criteria. For the first time, the McDonald 2010 criteria have included children (only presenting with CIS, not ADEM).

History of the development of McDonald magnetic resonance imaging (MRI) criteria in adults

In 1997, Barkhof et al (85) developed a model consisting of 4 MRI parameters (sample size, n= 74 patients) — the presence of ≥1 gadolinium-enhancing, ≥1 juxtacortical, ≥1 infratentorial, and ≥3 periventricular lesions. In 1999, Tintore et al (86) adapted these criteria by allowing the gadolinium enhancing lesion to be replaced by 9 T2 lesions and introduced the model of having at least 3 of the 4 Barkhof parameters to achieve a higher diagnostic accuracy and an improved balance between sensitivity and specificity for predicting conversion from CIS to clinically definite MS (CDMS).

In 2001, the 2001 McDonald et al (87) diagnostic criteria were published (Table 10). The MRI criteria chosen by an expert panel approved the models developed by Barkhof et al. and Tintore et al. with some modifications and additions. The 2001 McDonald criteria were retrospectively evaluated in CIS adult cohorts showing high specificity (83-86%) for clinically definite MS (CDMS) (88, 89) but limited sensitivity (49%)(90). In 2005, the McDonald DIS and DIT criteria(67) were then revised (Table 10). The 2005 McDonald criteria were compared to

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the 2001 criteria in adults and showed an improvement of sensitivity (60% vs 47%) while retaining a good specificity (88% vs 91%) (91). In 2010, The European Magnetic Imaging in MS (MAGNIMS) multicenter research network (92) compared the McDonald 2005 DIS criteria with simplified criteria developed by Swanton et al (91). In the Swanton model, DIS can be met with at least 1 T2 lesion in at least 2 of 4 locations (juxtacortical, periventricular, infratentorial, and spinal cord), with lesions within the symptomatic region excluded in patients with brainstem or spinal cord syndromes. In 282 CIS patients, the Swanton-based DIS criteria were slightly more sensitive than the original McDonald Criteria for DIS, without sacrificing specificity and accuracy (91). For DIT, it was shown that disposing of the requirement for an extra reference MRI after 1 month did not compromise specificity (93). In addition, MAGNIMS group (92) showed that in CIS patients, a single brain MRI study that demonstrates DIS and both asymptomatic gadolinium-enhancing and non-enhancing lesions is highly specific for predicting early development of clinically CDMS and reliably substitutes for prior imaging criteria for DIT (92, 94). Importantly, the revised criteria allow for MRI diagnosis of MS on a first gadolinium enhanced scan.

Table 10: McDonald MRI criteria adults

	McDonald 2001 (87)	**McDonald 2005 (67)**	**McDonald 2010 (22)**
DIS	3 or more of (a-d): a. ≥9 T2 lesions or 1 Gadolinium enhancing b. ≥3 periventricular lesion(s) c. ≥1 juxtacortical lesion(s) d. ≥ 1 infrantentorial brain lesion(s)*****	d. ≥ 1 infrantentorial brain lesion(s) OR ≥1 spinal cord lesion(s)*****	2 or more of: ≥1 periventricular ≥1 juxtacortical ≥1 infratentorial**§** ≥ 1 spinal cord**§**
	OR the presence of 2 or more T2 lesions plus CSF oligoclonal bands		
DIT	1 Gadolinium enhancing lesion at least 3 months after CIS onset **OR** A new T2 lesion with reference to a prior scan obtained:		>1 new lesion when compared to a previous scan (irrespective of timing).
	>3 months after CIS onset	>1 month after CIS onset	**Or** presence of asymptomatic enhancing lesion and a non-enhancing T2 bright lesion on any one scan

DIS= dissemination in space; **DIT=**dissemination in time.

*In McDonald 2001 1 cord lesion can replace 1 brain lesion; In McDonald 2005 any number of cord lesions can be included in total lesion count; AND spinal lesions equivalent to infratentorial lesions.

§ All lesions in symptomatic regions excluded in Brainstem and spinal cord syndromes.

History of the development of childhood MRI multiple sclerosis criteria

Different combinations of MRI characteristics have been proposed to aid in establishing the diagnosis of paediatric MS or to assess the risk of relapse after an initial event (Table 11 and Table 12). These MRI criteria were dissimilar to those used in adults, reflecting the differences in presentation of ADS and MS in children, and were developed for somewhat different purposes (95) and in different populations. The Kids With Multiple Sclerosis (KIDMUS) criteria (77), and criteria from a prospective Canadian cohort (96) aim to differentiate monophasic from relapsing disease at the time of the first clinical presentation of CNS demyelination from the baseline MRI (77, 85, 96). The Callen MS-ADEM criteria were developed to distinguish ADEM from MS (25). The Callen paediatric MS criteria were developed to distinguish MS from other neurological disorders, such as migraine, but excluding ADEM (97). Dissemination in time criteria have not been developed for children until the incorporation of the McDonald 2010 criteria.

Compared to adults, children with MS appear to have an increased T2 lesion load on MRI at disease onset (24, 98). The information obtained through cohort based natural history studies, suggests a higher level of inflammation in children (Figure 5). Data obtained through controlled trials might however be different than that through natural history control studies or registries, as there one may expect recruiting individuals with fewer less relapses and lower MRI T2 lesion.

Currently, conventional MRI is not a useful surrogate outcome marker for disease relapse or disability. Advanced neuroimaging methods have shown that injury begins earlier than previously believed (99-108). These techniques have started to be implemented in adult clinical trials (Barkhof et al., 2009), although standardising approaches has been challenging

and slower than desired. In parallel with an increasing use of advanced (quantitative) techniques, adult studies are also moving towards higher field strength, while the few paediatric studies to date (sample sizes n=20—46) have been carried out on 1.5T scanners (109-113).

 Advanced neuroimaging methods are increasingly used to understand disease processes in children (114, 115). One advanced technique, magnetization transfer ratio (MTR), reflects tissue integrity, which, in the context of MS white matter, is related to myelination (116) (not as yet assessed in paediatric MS). Combining techniques may provide synergistic information, hence better identifying the extent of disease and providing better biomarkers that one technique alone.

Table 11: Paediatric ADS and MS MRI diagnostic criteria

KIDMUS (77)	Callen MS vs. ADEM (25)	Callen Diagnostic MS (97)	Verhey Model (96)	McDonald 2010 (22)
1 of 2:	2 out of 3:	2 out of 3:	2 of 2:	2 or more of:
				≥1 periventricular
Lesions perpendicular to long axis of the corpus callosum	Absence of a diffuse bilateral lesion pattern	≥5 lesions on T2 weighted images	≥ 1 periventricular lesion(s)	≥1 juxtacortical ≥1 infratentorial ≥ 1 spinal cord
				AND
Sole presence of well defined lesions	Presence of black holes	≥2 periventricular lesions	≥1 hypointense lesion(s) on T1 images	≥1 new lesion compared to previous scan, OR presence of asymptomatic enhancing lesion and a non-enhancing T2 lesion on any scan
	Greater or equal to 2 periventricular lesions	≥1 brain stem lesion(s)		

Table 12: Paediatric ADS and MS MRI diagnostic criteria; sensitivity and specificity

KIDMUS (77)	Callen MS vs. ADEM (25)	Callen Diagnostic MS (97)	Verhey Model (96, 117)	McDonald 2012 (117)
Compared to Barkhof space criteria	Compared to McDonald 2005 space criteria	Compared to McDonald 2005 space criteria	Compared to McDonald 2005 space criteria	Compared to McDonald 2005 space criteria
Specificity: 100% vs 63%	Specificity: 95% vs 30%	Specificity: 98% vs 100%	Specificity: 90% vs 100%	Specificity: 80% vs 100%
Sensitivity 21% vs 52%	Sensitivity 81% vs 68%	Sensitivity 85% vs 76%	Sensitivity: 70% vs 74%	Sensitivity: 85% vs 74%

Figure 5: MRI brain and spine of a 15 year old adolescent female with clinically relapsing remitting Multiple Sclerosis (positive oligoclonal bands). There are multiple T2-weighted and FLAIR lesions; periventricular (A, D, F), juxtacortical (E), gadolinium enhancing on T1 (C), infratentorial spinal lesion spanning 2 vertebral cervical segments (B) hence fulfilling McDonald criteria.
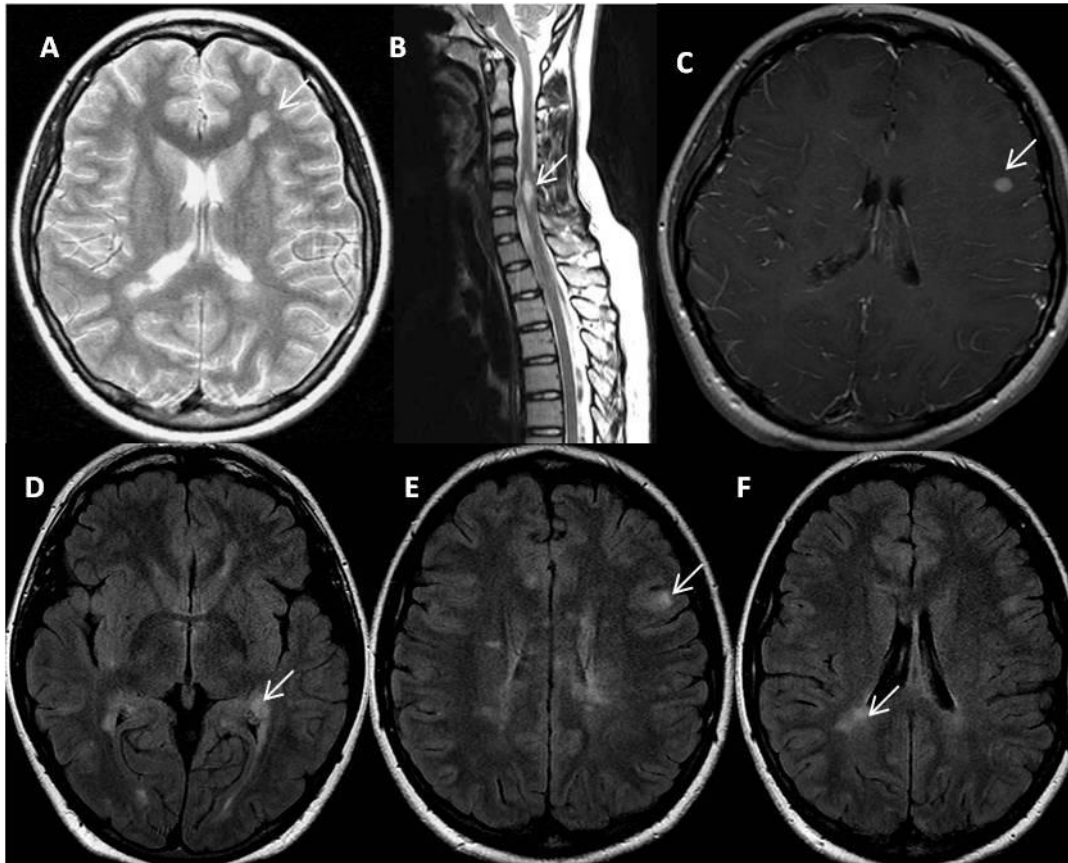
1.5 Immunological features, and investigative features in ADS and MS

Immunological Features

There is a paucity of information with regards the immunopathology of paediatric MS and the consequences of ongoing neurodevelopment and changing immune systems which may contribute to differing natural history than adult onset MS. Mounting information regarding risk factors for both adult and paediatric MS point to similar influences; however, the timing of exposures, particularly infectious exposures, and the extent of effect may be different.

The cause of CNS Inflammatory demyelination is still unknown, and no biomarker has been established for ADEM or MS diagnosis.

Pathologically, ADEM is characterized by perivenular infiltrates of macrophages, lymphocytes, and plasma cells with demyelinated and oedematous neighbouring white matter. Lesions are multifocal and usually diffuse being found in predominantly white matter of brain, optic nerves, and spinal cord. Deep grey nuclei are sometimes affected. Typically, and differently to MS, lesions are of the same age, and there is usually minimal axonal injury (118).

Multiple Sclerosis is a chronic inflammatory demyelinating disease of the CNS characterized by myelin loss, axonal degeneration and, often, progressive neurological dysfunction.

Idiopathic TM is an inflammatory demyelinating condition with immune mediated mechanisms implicated. Numerous case series have reported a large number of patients having CSF pleocytosis and raised CSF proteins (43, 44, 46, 51, 52). Histopathological studies

have demonstrated focal infiltration of the spinal cord by monocytes and lymphocytes as well as astroglial activation (49). Grey and white matter have been observed to be equally affected, confirming recent MRI observations (46).

Several immune mechanisms have been postulated. In healthy CNS, immune surveillance involves both immune cells entering and possibly leaving the CNS, and antigen draining from the CNS in to the periphery [reviewed in (119, 120)]. Activated T cells can migrate across the blood brain barrier (BBB), facilitated by a host of endothelial and local factors (121). Under normal conditions this lymphocyte surveillance activity does not lead to inflammation or alter BBB integrity (119, 122). However, when patrolling lymphocytes, in the context of local infection or autoimmune disease, re-encounter their specific antigens in the CNS (presented via perivascular antigen presenting cells), they may initiate a classical "auto-inflammatory" response. The response promotes BBB disruption and invasion of high numbers of activated lymphocytes into CNS parenchyma (123). These mechanisms form the cornerstone of our current thinking on the induction of disease in CNS autoimmune disorders [reviewed in (124)].

Additionally, although many reports have quoted childhood infections and immunisations as temporal associations, studies have not included an appropriate design such as large case control studies. If these associations are confirmed, it remains uncertain whether the link with TM is a result of molecular mimicry (immune targeting of infection/ vaccine related proteins that bear molecular similarity to neuronal proteins), or whether the heightened immunity increases the pool of T or B cells clones which possess the ability to recognise neuronal proteins (42) or a combination of the two.

Immune system: possible insights from studying ADS in children

In a recurrent form of demyelination, neuromyelitis optica (NMO), the antibody to aquaporin 4 (AQP4) has recently been demonstrated to be a disease specific biomarker and to be pathogenic in animal models (125). The work on NMO raises the possibility that other autoantibody biomarkers may be present in other childhood demyelinating diseases. Antibodies to native myelin oligodendrocytes glycoprotein (MOG), uncommon amongst adult-onset patients (126), have been found in 38% of paediatric-onset MS patients and also in a cohort of patients with ADEM (127). These and other CNS directed antibodies may be determinants of childhood demyelinating disorders and that their identification may prove helpful in diagnosis and management.

Specific Investigations

Many inflammatory and non-inflammatory disorders may have a similar clinical and radiologic presentation and should be considered in the differential diagnosis as above. There are no formal guidelines as yet with regards the investigation of a suspected inflammatory CNS presentation. Investigations are tailored according to the clinical presentation and progress, consideration of differential diagnosis (see chapter 1.7), and MRI appearances.

CSF Oligoclonal bands represent intrathecal synthesis of IgG. Although they are not specific for inflammatory demyelination as they can be positive in other disorders, they are useful in supporting diagnoses.

Visual Evoked Potentials (VEPs) are useful in the assessment of demyelination of the optic pathways.

The presence in serum of antibodies directed against aquaporin 4 (NMO- IgG) appears to be sensitive and specific to paediatric NMO.

Approximately half children presenting with TM (a monofocal CIS) reported in the literature have CSF pleocytosis and/or raised protein levels. In isolated monophasic TM, CSF oligoclonal bands are normally absent (Table 13). In children, the TMCWG criteria may be too stringent, repeat investigations to confirm inflammatory criteria may not be appropriate and hence a diagnosis of probable TM may be made based on clinical presentation, investigation and MRI findings. Testing for NMO-IgG antibodies should also be considered at the outset for all children presenting with TM (see NMO sections in chapters 1.4 and 3.4).

In chapters 2, 3, and 4 and I will further explore in more detail the utility of investigative features to help characterise ADEM, CIS, NMO and MS.

.

Table 13: Summary of investigative and MRI features of TM

Ref	Alper 2010	DeGoede 2010	Kalra 2009	DaJusta 2008	Yiu 2008	Pidcock 2007	Defresne 2003
CSF pleocytosis/ raised protein	10/27 (37%)	16/36 pleocytosis (44%), 11/36 protein >0.4g/L	3/6 pleocytosis, 4/6 raised proteins	n/a	CSF (in 74%): 67% pleocytosis 38% raised protein	50% pleocytosis (17/34) raised protein in 48% (14/29)	15/24 pleocytosis 3/14 raised protein;
CSF OGB positive/ IgG index	0/22 OGB positive, 2/21 IgG index raised	4/27 OGB positive,	n/a	n/a	n/a	OGB positive or raised IgG index in <5%	0/14 OGB positive
NMO-IgG/ other antibody tests	0/5 positive	n/a	Anti-GM1 Abs in 46% with TM vs 6.6% control (P= 0.035)	n/a	n/a	n/a	n/a
MRI spine; segment lengths affected	segs (mean 6.4)	7/39 >6 segments	13/15 had >3 segs (2 entire cord)	n/a	68% had ≥3 segs (mean 8segs)	Mean segs=6 (1 multifocal, 1 entire cord)	4/6 had >2segs
MRI spine; regions affected	10 cervical ± thoracic, 6 thoracic, 1 lumbar, 4	14 cervical, 19 thoracic, 7 lumbrosacral;	thoracic cord most common; 1 multiregional	Cervical 57% Thoracic 43%	n/a	cervical 19/38, thoracic 15/38 , lumbar/conus 2/38 , 2/38 normal.	2/6 normal
MRI spine; GAD enhancement	4/21	n/a	2/4	n/a	n/a	74% (26/35)	3/6
MRI brain features	1/25 patchy T2 hyperintensity	17/26 abnormalities (6 symptomatic)	n/a	n/a	3/10 abnormal (2 asymptomatic, 1 brainstem extension)	n/a	1of 4 multiple T2 lesions in cortex and basal ganglia

Anti-GM1 Abs= Anti-GM1 antiganglioside immunoglobulin G antibodies; CSF= cerebrospinal fluid; GAD= gadolinium enhancement; IV= steroids; Neuromyelitis Optica; OGB= oligoclonal band; segs= segments;

1.6 Genetic-environmental associations in multiple sclerosis

Genetic and environmental risk factors are likely to be operating in ADS and MS immunopathology. Adult MS prevalence varies from very low rates in peri-equatorial regions, to over 100 per 100,000 population in temperate regions distant from the equator, hence prompting consideration of limited sunlight and vitamin D insufficiency as potential risk factors for MS. These features are yet to be shown in childhood ADS.

Genetic influence is childhood acquired demyelinating disorders compared to adults

There is increasing awareness of the importance of genetic factors that determine the host response to likely environmentally triggered childhood CNS immunological diseases (128). In adults the most important component of MS hereditability is situated in the Major Histocompatibility Complex (MHC). Recently, in a Canadian Paediatric study, HLA-DRB1*15 was shown to be significant (OR=3.3 p<0.001) for the development of MS (129). In adult onset MS, interactions between HLA haplotypes are key to determining MS risk, for example HLA-DRB1*08 has been shown to more than double the risk of MS associated with a single copy of HLA-DRB1*15 (130-133). Recent identification of mutations of *RANBP2* gene (encodes protein part of the nuclear pore complex) (134), thiamine transporter gene *SLC19A3* (135) and polymorphisms in the carnitine palmitoyl transferase II gene (136) in children with acute subtypes of recurrent encephalopathy raises the possibility of these or other genes being involved in pathobiology of ADEM and MS. These mutations may indeed contribute to a subgroup of children with demyelination.

Geographic Distribution pointing towards environmental influences

MS has long been believed to be a disease with rates rising with increased distance from the equator in both northern and southern hemispheres (137). However, data on the geographic distribution of MS in children are lacking, and it is yet to be determined whether paediatric cases of MS follow the same pattern. Preliminary data suggest that non-Caucasian ancestry may play a role in paediatric MS. Childhood populations in the United States and Canada have a higher than expected number of MS patients under age 18 who are first generation North Americans with parents born in either Latin or Caribbean countries, where MS is usually less common (138, 139). Migration studies hence imply that puberty is a decisive stage for changing the risk of developing MS (140).There is evidence that Indian and Pakistani immigrants who entered England younger than 15 years of age had a higher risk of developing MS than those that entered after this age (141).

Vitamin D

Vitamin D has become increasingly topical and one interesting factor appears to involve sunlight and vitamin D (142, 143).

The amount of winter sunlight parallels the range of MS prevalence, and high sunlight exposure is associated with low disease prevalence [69]. Sunlight, through its responsibility in generating active vitamin D, has hence been proposed as a potential significant environmental factor for the disease. Recently, sequence analysis found a single MHC vitamin D response element (VDRE) to the promoter region of HLA-DRB1, which was conserved in HLA-DRB1*15 haplotypes but variant to some extent in all others (144).

Vitamin D has also been postulated to be important in early brain development (145). There has hence been increasing speculation that gene-environment interactions could lead to preventive interventions in at risk individuals (146, 147). For example, a Norwegian study demonstrated reduced risk for MS in adults reporting an increased amount of childhood outdoor activities (148).

Infectious Agents and vaccination

Ebstein-Barr Virus (EBV) has been implicated to have a role in increased MS susceptibility. A case control study in Toronto showed that 83% of 30 paediatric MS patients had serologic evidence for remote Epstein-Barr virus (EBV) infection, compared with 42% of 90 controls, suggesting a potential increased risk of paediatric MS being associated with EBV infection (149). These findings have been confirmed in a German (150) and in a multinational cohort (151). A large population-based study, showed the rate of previous infection with infectious mononucleosis at approximately 50% of MS cases compared to 20% (p<0.001) of controls (152). Similarly the group have also shown that historically reported measles, mumps, rubella, varicella and vaccination for hepatitis B, influenza, measles, mumps and rubella are not associated with increased risk of MS later in life. A recent large cohort study also showed no correlation between hepatitis B vaccination and paediatric MS(153). *Chlamydia pneumoniae* antibodies have been detected in CSF of paediatric (154) and adult MS patients (155) but the significance of these findings is uncertain (156).

Epidemiological studies have shown that exposure to siblings in the first 6 years was associated with a reduced risk of MS, possibly due to altered developmental immune responses(157).

1.7 Differential Diagnosis

The differential diagnosis of multiple sclerosis is wide and even more so in children compared to adults. Two relatively recent review articles have reviewed the issue in both children (28) and adults (27), although the likely diagnoses in children with white matter abnormalities is likely to be even wider.

Many inflammatory and non-inflammatory disorders may have a similar clinical and radiologic presentation and should be considered (guided by clinical presentation and MRI findings) in the differential diagnosis as highlighted in Table 14.

When the MRI shows large focal tumour-like lesions, one should consider brain tumours, brain abscesses, and variants of ADEM/MS. An MRI pattern with symmetric bithalamic involvement may be seen in children with acute necrotizing encephalopathy, deep cerebral venous thrombosis, hypernatremia, and extrapontine myelinolysis. Basal ganglia involvement may be consistent with organic aciduria, poststreptococcal infection, or infantile bilateral striatal necrosis. The presence of complete ring-enhanced lesions in the cerebral white matter is unusual in ADEM, and brain abscess, tuberculomas, neurocysticercosis, toxoplasmosis, and histoplasmosis should be excluded. Vasculitic lesions may also mimic inflammatory demyelination.

In Chapters 2 and 3 I further explore the differential diagnoses of ADS in a prospective cohort.

Table 14: Diagnoses to consider exclusion depending on presentation in children presenting with CIS or MS like phenotypes

System	Disorders
Endocrine	Thyroid disorder, diabetes mellitus
Inflammatory	Systemic lupus erythematosus, neurosarcoidosis, antiphospholipid antibody syndrome
Mitochondrial	MERRF, MELAS, LHON
Leukodystrophy	Metachromatic leukodystrophy, adrenoleukodystrophy
Genetic/metabolic	Inborn errors of metabolism, amino acidurias
Infectious	Herpes simplex encephalitis, post streptococcal infection, HIV, lyme disease, neurocysticercosis, Neuroborreliosis, brain abscess
Vascular/thrombotic disorders	CADASIL, Moyamoya disease, carotid dissection, Cerebral venous sinus thrombosis, other vasculitis or vasculopathies
Nutritional	B12 or folate deficiency
Neoplastic	Lymphoma, astrocytoma
Haematological	Hemophagocytic lymphohistiocytosis
Other	hypernatremia, extrapontine myelinolysis

MERRF: myoclonic epilepsy with ragged red fibers; MELAS: mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; LHON: Leber hereditary optic neuropathy; CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

1.8 Treatment

Acute demyelination

There are no controlled trials for the treatment of ADS in childhood. Most recommendations are mainly extrapolated from case series or data from clinical trials for the treatment of exacerbations of adult MS (41, 50, 158). In adults, treatment of relapses with IV methylprednisolone (IVMP) shortened relapse duration and sped up recovery. High doses of IVMP (more than 500 mg/day for at least 3 days in adults) are superior to lower doses (159). Children are usually treated with high dose intravenous steroids for 3-5 days to attenuate inflammation. There is consensus that intravenous corticosteroids should be administered in order to shorten the acute inflammatory process and hasten recovery. Subsequent oral steroid taper with a duration of 2–6 weeks is recommended for ADEM. In children who do not respond to steroids, intravenous immunoglobulin is often used, although the data to support this is limited to small case series and single case reports (5). Intravenous immunoglobulin (IVIg) is used at doses of up to 2 g/kg administered over 2–5 consecutive days. In children with severe symptoms not responding sufficiently to a first course of high-dose corticosteroids, a second pulse might be warranted , and in case of severe or life-threatening acute demyelination, plasma exchange should be considered. Plasmapharesis is increasingly used as rescue therapy based on its efficacy in a small randomised controlled trial in adults with acute CNS demyelination (160).

Disease Modifying Treatment in MS; children vs adults

Early initiation of "disease modifying agents", such as beta interferon and glatiramer acetate appears to be of benefit in adults. Thus, it is more critical than ever to accurately diagnose

MS as early as possible. However, very little is published on the use of interferon in children (161-165).

There have been no randomised controlled trials in ADS or MS conducted in children. Treatments are currently based on clinical experience and consensus. Differences in pharmacodynamics pharmacokinetics and of disease modifying treatments in younger patients are likely to be present, although there is little information available for the different drugs used in treatment of MS in children.

In the UK, it often difficult to obtain funding for traditional MS disease modifying drugs (Absoud et al; abstract presentation- "Immunomodulatory drug treatment in childhood MS: Experience from the UK." Eur J Paediatr Neurol 13:0; S103 (2009). I reviewed cases in 3 UK tertiary Centres to evaluate efficacy, safety and tolerability of immune modulating therapies (IMT) in childhood MS. In a retrospective UK audit survey from 3 UK paediatric demyelination clinics (2004-2008), 28 relapsing-remitting MS cases (22 female) with a mean age of 11 yr9m (SD 3yr6m) were ascertained. On presentation 50% had polyfocal clinically isolated episodes (CIS), 39% monofocal CIS and 11% acute disseminated encephalomyelitis (ADEM). Twenty-six were treated with interferon beta 1a or 1b (Rebif/Avonex/BetaInterferon) and 2 with glatiramer acetate (Copaxone). One patient stopped shortly afterwards (poor compliance). In one centre (12 cases) time from "decision to treat" to administering IMT averaged 5 months, and was due to delays in specific drug approval, and nursing support. These treatments are generally well tolerated There were no serious side effects. 29% reported flu-like symptoms, 25% fatigue, 18% transient

lymphopaenia, and 11% transient transaminasemia. Disease modifying treatments in childhood MS in this cohort appeared safe, well tolerated, as comparable to other childhood surveys and adult data (5). There is no European and indeed international consensus that recommends the use of first line treatments for paediatric MS and there is a need for future randomised clinical trials in children (166, 167).

Early referral to a specialist is essential for consideration of treatment in recurrent demyelination. Although recent research in adults suggests that early disease modifying treatment (DMT) of MS (such as such as with beta interferon and glatiramer acetate) may be beneficial, current criteria from the UK National Institute of Clinical excellence (NICE) do not support treatment for patients younger than 18 years of age as there are no large randomised trials in children. Observational case series suggest that DMTs in childhood MS appears safe, well tolerated, and efficacious (by reducing relapse rate) as compared to adult data. Neuromyelitis Optica is often treated with other DMTs (azathioprine, Rituximab) and hence the importance of early diagnosis.

It is beyond the scope of this thesis to detail current and future therapies in the pipeline, and referral should be made to the Paediatric Neurologist for consideration of these therapies.

Treatment of NMO

It is important to recognise NMO early in the course of the disease as permanent disability is more attack-related in NMO than in MS (168). Hence, early and aggressive intensive treatment with disease modifying treatment may be beneficial in reducing the disability and ameliorating the course of disease in children (27, 61, 68, 69, 168). There have been no large

randomised trials in children or adults and current practice is based on case series and expert opinion. Recent adult European consensus guidelines have been published (168). In children, acute exacerbations are usually treated with 5 days of intravenous steroids ± intravenous immunoglobulin. Severe exacerbations are treated with plasmapheresis. A wide variety of disease modifying drugs have recently been used but recent reports show that drugs used to treat multiple sclerosis (interferons, glatiramer) may exacerbate NMO (169). Future clinical trials incorporating children are needed in this condition.

1.9 Outcome, MS & Risk of Relapse

The first episode of CNS Inflammatory Demyelination may occur as an isolated monophasic illness or may represent the first attack of MS (Figure 6). Several studies have been conducted to establish clinical and radiological risk factors for MS development after a fist attack of CNS inflammatory demyelination (Table 15). Most of these studies although longitudinal, were conducted before international definitions (2007), and had a retrospective case ascertainment from tertiary centres and hence subject to bias. Hence the risk factors currently reported in the literature and summarized here need to be interpreted with caution. No clinical features, radiological, serum, or cerebrospinal fluid (CSF) biomarkers absolutely distinguish ADEM or isolated CIS form MS and further research in this area is ongoing. Radiological MRI criteria have also been suggested for children which are yet to be established in longitudinal prospective studies. The majority of paediatric onset MS is characterised by a relapsing remitting course (figure 3) and later into adulthood becomes secondary progressive.

Table 15: Risk Factors of Multiple Sclerosis after a first CNS inflammatory demyelinating event.

Increased Relapse risk	Decreased relapse risk
>10 years of age	<10 years of age
CIS- polyfocal	ADEM
Optic neuritis	Isolated Transverse Myelitis
No encephalopathy	Encephalopathy
CSF oligoclonal band positive	Presentation with meningism, fever, seizures
MRI brain showing asymptomatic lesions	MRI brain without symptomatic lesions

Risk of MS in ON

Optic neuritis (ON) is one of the most common CIS events in children. Bilateral optic neuritis is more common in children than adults (approximately half of childhood optic neuritis is bilateral). Despite severe acute visual loss, approximately 70-80% of children will recover visual acuity (snellen of 6/9 or better). Both unilateral and bilateral optic neuritis can be the first manifestations of MS or Neuromyelitis Optica. In recent studies of children with optic neuritis , 20-45% experienced further demyelinating attacks leading to a diagnosis of MS after follow-up periods of approximately two years. Recurrent optic neuritis and the presence of MRI brain lesions extrinsic to the optic nerves has been associated with an increased likelihood of MS after ON onset.

Outcome of TM

Children are thought to have a better outcome than in adults (44, 51, 170) with approximately half making a complete recovery. However, a group of children have severe disabilities. Additionally deaths have been reported mainly due to respiratory failure associated with a high cervical cord lesion (43, 51, 53). The most common sequelae affecting children are sensory disturbances and bladder dysfunction (15-50%). Approximately one quarter are wheelchair-bound or require an aid for walking. A group of children never regain mobility or bladder function (10-20%). Several studies have attempted to correlate presenting clinical and laboratory features with clinical outcome (Table 16). A higher spinal level is the only consistent poor prognostic feature across these studies. An identifiable trigger (intercurrent illness or vaccination) does not appear to predict clinical outcome. The influence of age, rapidity to nadir of symptoms and late start of recovery in predicting clinical outcome appear to vary between studies.

TM may be isolated or part of a polyfocal clinically isolated syndrome (CIS). It can be monophasic, or later relapse and hence be the first presentation of a relapsing NMO spectrum (Figure 1) disorder or Multiple Sclerosis (Figure 2). Patients with TM should be followed up longitudinally irrespective of initial outcome, in part to clarify the diagnosis and to provide ongoing multidisciplinary support into ongoing rehabilitation (motor, sphincter, psychological, and schooling support).

Table 16*: Summary of poor prognostic factors reported in recent case series for paediatric TM (43, 44, 51, 52, 171)

Ref	older age (>10)	rapid onset to nadir<1day	late start of recovery>1 week	higher spinal levels	Sphincter involvement	flaccid legs at presentation	many spinal segments	CSF pleocytosis	intercurrent illness/ vaccination
DeGoede 2010	yes	Yes	yes	Yes	Yes	Yes	n/a	n/a	No
Yiu 2009	No- younger age	No	n/a	Respiratory failure requiring ventilation	n/a	Yes	No	n/a	n/a
Pidcock 2007	No- younger age	No	n/a	Yes	n/a	n/a	yes	yes	No
Defresne 2003	n/a	Yes	n/a	n/a	n/a	Complete paraplegia	n/a	n/a	n/a
Miyazawa 2003*	No- younger age	No	n/a	n/a	n/a	No Babinski's reflex	n/a	n/a	No

* Compilation of 50 case reports from Japan (1987-2001)

Transverse Myelitis and risk of Multiple Sclerosis

The International Paediatric MS Study Group defined paediatric MS as requiring multiple episodes of CNS inflammatory demyelination separated in time and space as in adults. Dissemination in time can be met if new T2 or gadolinium enhancing lesions develop 3 months following the initial clinical event. Dissemination in space can be met by one of the following:

(i) The revised McDonald criteria for a "positive MRI" are applied; with 3 of: 1) >8 white matter lesions or one gadolinium enhancing lesion, 2) >2 periventricular lesions, 3) a juxtacortical lesion, 4) an infratentorial lesion

(ii) The combination of an abnormal CSF (oligoclonal bands or elevated IgG index) and 2 lesions on the MRI (at least one in brain).

When compared with other CIS presentations, isolated TM carries the lowest risk of progression to MS (15, 51). Studies examining the relation of TM with polyfocal CIS and MS are sparse. Case series in TM have also reported that a number of patients have asymptomatic brain lesions (Table 7). In a French cohort of children with a first attack of CNS inflammatory demyelination, 7% (2/29) with a monofocal TM at presentation were later diagnosed with MS (15). Another series reported only 2% (1/47) of TM cases progressing to MS (43). However, 31% (13/42) of children with polysymptomatic clinical features including transverse myelitis at presentation were later diagnosed with MS (15). This highlights the importance of differentiating isolated TM from TM that is part of a polyfocal syndrome.

In adults with MS, spinal lesions are usually less than two segments and located in the posterolateral aspect of the spinal cord (46, 172, 173). A recent adult study (174)found that 50% of patients converted to clinically definite MS when they had the combination of TM and brain lesions [Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study Criteria (175); >1 brain lesion >3mm in diameter with ≥1 periventricular or ovoid]. Children with MS have also been shown to tend to have spinal lesions less than 3 segments (see Figure 4), although longer segments (LETM) have been reported to progress to MS as well (65). Further prospective studies with longer term follow-up are needed to clarify this.

Outcome in NMO

Paediatric NMO appears to have a better prognosis than adult NMO in terms of disability. In one study median time from onset to EDSS 4 (20.7 vs 5.3 years; p <0.01) and EDSS 6 (26 vs 8.5 years; p <0.01) was largely explained by the increased severity of the first myelitis in the adult NMO group (69). In contrast, the USA paediatric NMO-spectrum series showed residual disability in 43/48 patients (90%) with 54% having visual impairment (27% blind) and 44% motor deficits (median Expanded Disability Status Scale 4.0) at 12 months (71). Further prospective longitudinal studies are needed to clarify these findings.

Figure 6: Risk of childhood MS after a first attack of CNS Inflammatory Demyelination (RDEM: Recurrent ADEM; MDEM: Multiphasic ADEM)
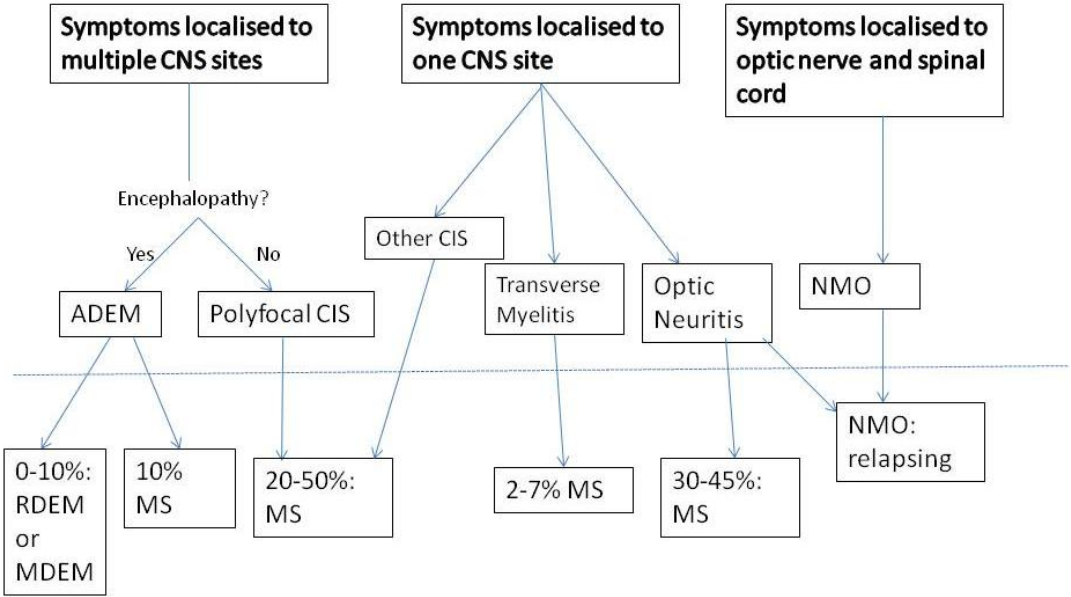
1.10 Neurodisability

A systematic review of the natural history of MS showed the most commonly reported physical and cognitive effects of the disease include: weakness, fatigue, ataxia, bladder complaints, bowel problems, sensory effects and visual impairment (34), illustrated in Figure 7. The most reported and quoted tool for the grading of functional effects of MS in adults is the (Expanded) Disability Status Scale (EDSS). The scale ranges from 1 (least severe) to 10 (death from MS). However, the scale is not ideal because there is a bias towards the physical effects of the disease (particularly ambulation) rather than the cognitive effects. Relapse rates in relapsing-remitting MS vary considerably over time for an individual and between individuals, but there is a general pattern of exacerbations of more frequent relapses, followed by long periods of lower rates. This makes assessment of the effects of treatments in an individual extremely problematic.

Children, compared to adults, frequently have slower disability as progression measured by EDSS but reach disability levels at a younger age than individuals with adult onset MS (11, 83, 176, 177). A large French study utilising data collected from 13 adult neurology departments via the European Database for Multiple Sclerosis (EDMUS) database identified a cohort of 394 patients who had multiple sclerosis with an onset at 16 years of age or younger and compared disability outcomes to 1775 cases who had adult onset multiple sclerosis. Time to secondary progression which heralds sustained build up of disability, independent of any relapse was one of the key outcomes measured.

The median time from onset to secondary progression was 28 years (median at 41 years of age) for childhood onset MS compared to 19 years (median at 51 years of age) for adult onset MS . The median time from onset to disability score of 6 (ability to walk with unilateral

support no more than 100 m without rest) was 28.9 years (42.2 years of age). Age hence appears to be a major determinant of remyelination efficiency given that myelin destruction is an early observation in the disease course (178, 179).

Cognitive deficits

In comparison to adult-onset MS, the examination of cognitive functioning in paediatric ADS and MS, have been limited to a few small studies. Nevertheless, there is emerging evidence that children with MS, compared to adults, more frequently have cognitive deficits (180, 181). Children may be particularly susceptible to cognitive impairment since the pathological processes affecting a developing central nervous system can also impinge on neural networks important for learning and language. In addition, neurodevelopmental co-morbidities often occur in young people who develop an acquired neurological disease (182). The prevalence estimates of intellectual impairment in childhood ADEM, CIS and MS range between 20 and 50% of patients (183, 184). As in adult onset MS, the most common impairments involve information processing speed, working memory, and executive functioning. Other aspects affecting children not highlighted in adult onset MS include a greater impact on overall IQ and also effects on language (185, 186)). As to be expected, intellectual functioning in children is most strongly correlated to the overall level of disability as measured by EDSS (183). Despite this, one study documented worsening cognitive functioning in over half of patients with MS, unrelated to worsening overall disability as measured on EDSS(187).

Currently, conventional MRI cannot fully explain the neurocognitive impairment which is the earliest feature of neurodegeneration in children with MS. Advanced neuroimaging methods have been shown to be more sensitive to the evolution of MS damage in adults over time

and show that injury begins earlier than previously believed. These techniques have started to be implemented in adult clinical trials (188), however standardising approaches for use in multicentre studies has been slow. In addition all paediatric studies have only been carried out on 1.5T scanners which result in longer scanning times and inferior quality (109-113). Additionally, these paediatric studies have only recruited relatively small numbers (20-46 cases). Paediatric studies have reported an association between cognitive function and: reduced size of thalamus; global brain volume; and white matter integrity and microstructure as measured by fractional anisotropy (189, 190). Overall cognitive deficits associated with paediatric ADS affects school attendance, participation, and performance (191).

Figure 7: Outcome issues

Child with Demyelination

cognition

attention

Schooling

behaviour

fatigue

participation

disability
- motor
- vision
- continence

Adult with MS

independence

vocation

Reproduction and parenting

treatment

Transition
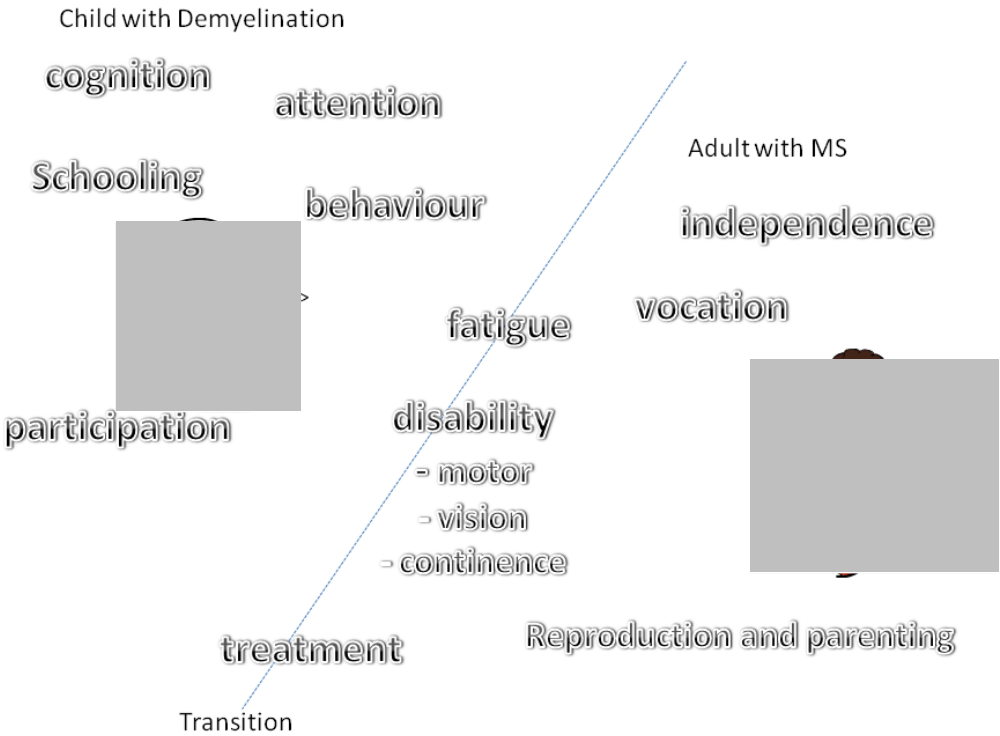
1.11   Conclusions

ADS and MS occur in children as well as adults. The presentation differs in children and adults, hence specific operational diagnostic criteria have been developed for children. Relatively little is known about the aetiology, incidence and prognosis of these conditions when presenting in childhood however. There is no randomised control trial evidence to support the treatment of children, and as highlighted the differences between adult and paediatric MS do not support a straight forward extrapolation from results obtained in adults. Evidence on incidence, natural history, imaging features prognosis and outcomes is required to inform trial design as well as to inform gaps in clinical and epidemiological evidence on ADS and MS in children.

In the subsequent chapters I will describe a national ADS incidence study I set up which uses multiple sources and two well established active surveillance units. This prospective surveillance study has also integrated detailed review of MRI images and investigative features combined with the robust application of International Paediatric Multiple Sclerosis Study Group (IPMSSG) consensus definitions (using additional help of an expert panel for inclusion, exclusion and differential diagnoses). I will then report on the one year outcomes and describe demographic clinical, investigative and MRI risk factors for relapse. In the following chapter, I will discuss the set up of a prospective cohort and the methodological considerations needed for clinical trials and preventative trials in ADS. I will conclude with implications and directions for future clinical and research practice in the UK.

CHAPTER 2: INICIDENCE, CLINICAL AND MRI FEATURES OF ADS

2.1   Study Aims

In this chapter, I report a multinational multisource prospective active surveillance study in the British Isles (latitudes 50-59 degrees) with the primary objective of determining the incidence of fist presentation of childhood CNS inflammatory demyelinating disorders in the UK and Ireland. Secondary objectives were:

- to report clinical features, and distribution by age, sex and ethnic group

- to report the clinical, investigative and MRI features of childhood ADSs using expert panel review to apply IPMSSG consensus definitions (including the incorporated McDonald MRI 2001 and Barkhof space diagnostic criteria).(12, 192)

- to apply the newly revised 2010 McDonald space and time diagnostic criteria;(22) and the recent Verhey MRI prognostic MS criteria.(193)

- to identify the frequency of proposed for MS in children.

- to determine whether these children can be classified according to the new international classification and further characterise those that cannot.

- to evaluate the prevalence of AQP4 and other CNS directed autoantibodies in childhood ADS.

- to describe current practices and treatments offered in the UK and Ireland and increase awareness amongst practicing clinicians.

2.2   Study Methods

Study Design

I carried out a prospective active surveillance study of first episode ADS in children aged between 1 and 15 years and 11 months of age, in the British Isles with multisource ascertainment using two well established surveillance units in order to establish incidence of new cases arising in the period September 2009 to September 2010.

The British Paediatric Surveillance Unit (BPSU); primary source of data

The British Paediatric Surveillance Unit (BPSU) is a unit within the Royal College of Paediatrics and Child Health which facilitates epidemiological surveillance for rare childhood diseases of public health importance in the UK and Republic of Ireland. It is funded by the UK Department of Health. The BPSU was launched in 1986 by the Royal College of Paediatrics and Child Health, the Health Protection Agency and the University College London-Institute of Child Health (London) and is operated in cooperation with the Health Protection Scotland (HPS) and the Faculty of Paediatrics of the Royal College of Physicians of Ireland. The BPSU is funded by the Department of Health.

The BPSU has helped initiate over 80 studies with a card return rate consistently higher than 93% (194). The BPSU system lessens the burden on practising clinicians of requests from numerous different sources. The BPSU also aims to increase clinicians and public awareness of rare disorders and improve prevention, treatment and service planning. Central to set up of a study is patient and public involvement.

The Process (see Figure 8):

1. One month before commencing the study a protocol card and letter is sent to all clinicians informing them of the study.

2. An Orange Card with a list of disorders is sent monthly to more than 3200 consultant paediatricians and other specialists.

- Clinicians return the card to the BPSU notifying any cases or 'nothing to report'

- A tear-off slip is provided for paediatricians to keep a record of patients reported.

- Clinicians are contacted by study investigators with a short questionnaire, and requests for supplementary investigations.

- Investigators inform BPSU if the case report fits the case definition.

Approximately 3200 clinicians in the UK and Ireland are sent an orange card. The aim is to involve every senior doctor who is likely to have clinical responsibility for children with rare conditions. The following receive the orange card:

- All UK and Republic of Ireland Consultant Paediatricians

- Associate Paediatric specialists (with their own case load)

Two-phase BPSU application procedure:

- A short initial Phase 1application submitted to the BPSU Executive committee.

- Studies are required to fit the eligibility criteria:

  o the condition has low incidence (less than 300 cases a year) and requires national ascertainment of cases to generate sufficient numbers for study.

  o it addresses the epidemiology of a condition and/or variations in practice

- o is of scientific or public health importance

- o use additional alternative data sources

- A more detailed phase 2 application is submitted.

- Requires the submission of the research questionnaire, details on costing and administrative support available.

Consent & Confidentiality:

- The BPSU requires study applicants to detail the security measures in place to protect patient confidentiality

- BPSU studies are approved on the basis that there is no patient contact and consent is not sought.

- BPSU studies are required to collect minimal identifier information in order to discount duplication. To comply with Section 251 of the NHS Act 2006. BPSU studies therefore require approval from the National Information Governance Board's (NIGB) Ethics and Confidentiality Committee (ECC).

- NIGB applications that have BPSU approval go through a fast track process so there is little delay. Approved applications are placed on the Section 251 Register. Approved applications are reviewed annually.

Cost:

There is an administrative charge of £10,000 for undertaking a study through the BPSU. There is an additional charge for the cost of the protocol card production (approx £500).

Figure 8: BPSU Methodology
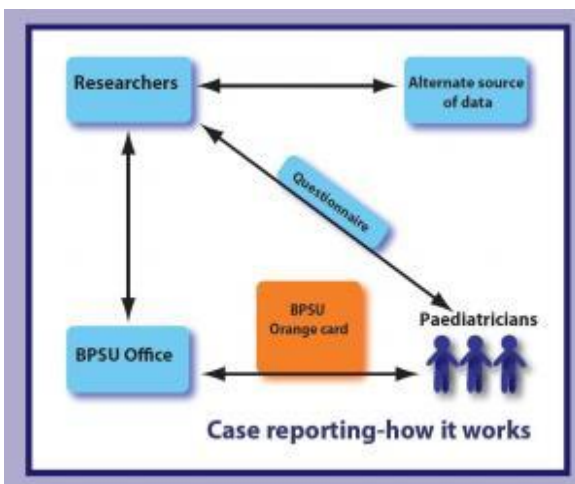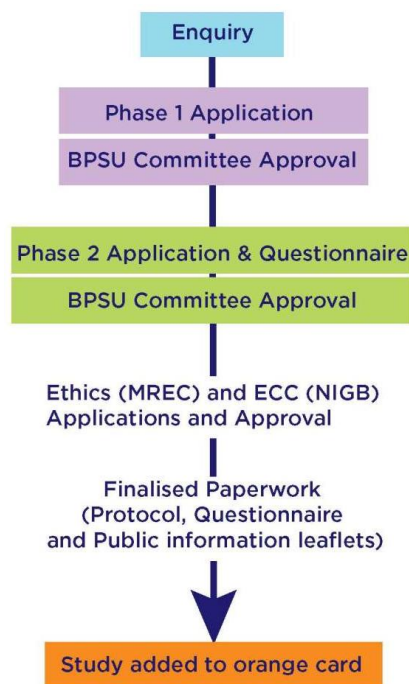
The British Ophthalmological Surveillance Unit (BOSU); alternative source of data for optic neuritis cases

The British Ophthalmological Surveillance Unit (BOSU) was set up by the Royal College of Ophthalmologists with support from the Fight for Sight charity. It enables ophthalmologists to participate in the nation-wide surveillance of uncommon ophthalmological conditions. The BOSU operates similarly to the BPSU and has a card return rate consistently higher than 75% (195).

The unit relies upon a monthly response from consultant and associate specialist ophthalmologists in the United Kingdom about new cases of the conditions stated on the BOSU Reporting Card. When a respondent reports a new case of one of the conditions under study BOSU will pass this information on to the researcher for investigation. Details of conditions included in the reporting scheme are given in study protocols.

 The principal aims of BOSU are to involve ophthalmologists in the surveillance of rare conditions of public health importance and research into uncommon ophthalmological disorders so that research can help in the improvement of prevention, treatment and service planning strategies of rare ophthalmological conditions. The provision of a unified system lessens the burden on reporting ophthalmologists of requests from numerous different sources for reporting cases of uncommon disorders.

A gold report card containing a list of conditions being surveyed is sent every month to all respondents on the mailing list (The card used for this study is reproduced in Figure 8). The mailing also includes reporting instructions and, where appropriate, protocols for new studies. The reporting clinicians are asked to tick boxes against any of the reportable conditions they have seen in the preceding month, or tick the "Nothing To Report" box if

none have been seen, and return the card to BOSU. A detachable slip is attached to the card for the ophthalmologist to keep a convenient record of patients reported.

"Positive" returns are identified by the Unit and then the appropriate investigator is notified. The investigator will then contact the reporting clinician directly to request completion of a brief questionnaire or permission to review case notes. Further research including enquiries to the patient is undertaken only with the permission of the ophthalmologist and, where appropriate the patient's GP.

The mailing list of approximately 1000 Consultant Ophthalmologists, Associate Specialists and Senior Lecturers in Ophthalmology has been developed and is systematically updated. The aim is to involve every senior doctor who may have clinical responsibility for patients with rare ophthalmological conditions.

Case ascertainment via active surveillance

One month before commencing the study, a protocol card and letter was sent to all clinicians informing them of the study. Monthly notification cards (mean per month 4095) were sent by the BPSU (mean per month 2945) to all registered Consultant Paediatricians, Paediatric Neurologists, and BOSU (mean per month 1150) to all registered Ophthalmologists (between September 2009 and September 2010 (13 months). In the UK, these clinicians are likely to see all cases of ADS. Clinicians returned the card to the surveillance units notifying any cases or confirming 'nothing to report.' Upon receipt of a positive notification the surveillance units provided the investigating team with a BPSU/BOSU case number, clinician name and contact details. The study team then contacted the clinician directly, sending a detailed data collection form and a blank CD for an anonymised MRI. As more than one clinician might notify the same patient seen in different settings, minimal identifiers

(National Health Service [NHS] number, district postcode, sex and date of birth) were used for record linkage and to exclude duplicates with a high level of certainty (www.rcpch.ac.uk/bpsu accessed 12/02/2012).

Rationale for study design

Epidemiological surveillance methods for these rare conditions are essential to for full case ascertainment if the full extent is to be realised. Missed cases will introduce a bias in estimating incidence. To avoid this, approval to collect pseudo-anonymised data without individual patient consent was deemed essential.

The UK & Ireland has robust surveillance systems and mechanisms for a national population based study.

To avoid this, approval to collect pseudo-anonymised data without individual patient consent was deemed essential. Permission was sought from the National Information Governance Board (NIGB).

ADS conditions and Multiple Sclerosis are rare disorders in the UK (and the overall number of cases reported through the surveillance units was expected to be small (e.g. 200-250/ year). If a large number of patients/parents/guardians do not consent to participate in the study, there will be uncertainty about the true incidence of these conditions. Furthermore, should consent to participate be lower within specific subgroups (e.g. children with different ethnicity, ages, socio-economic backgrounds), then this will introduce important bias in case ascertainment and may obscure conclusions about the epidemiology of these disorders. To obtain consent for participation, it may be necessary for the responsible clinician to await the next patient visit to obtain formal, written consent. This creates an additional burden

step in case ascertainment. To attain a high level of case ascertainment, it is not practicable to rely on reporting of cases after formal written consent has been obtained.

As with other epidemiological studies, complete case ascertainment may be difficult due to some cases not being reported or sub-clinical. This will be addressed by using clear internationally accepted and also multiple sources for case ascertainment.

Confidentiality and Ethics:

Data Protection Act and Caldecott guardian requirements were observed. Type A data (identifiers needed only for removing duplicates and corresponding with clinicians, i.e. NHS numbers) will be destroyed as soon as data collection has ended (including follow information). Type B data, the clinical data used for research which may also include patient identifiable data (e.g. date of birth, sex, that are also important for the data analysis) cannot be removed from the questionnaires and will be stored for 20 years in secure archives (MRC guidelines).

Funding:

Funding for a three years fellowship was secured from the UK MS Society and The Action Medical Research Charity.

Public involvement:

The study has been informed by consultation with various parties (including patients) at the first UK childhood MS conference hosted by the MS Society on 7th November 2007 in London. I have also recruited a lay representative from the MS Society in the study team to ensure that patient and family views are appropriately sought throughout the study. The lay

representative has also helped in design of the patient information leaflet (www.rcpch.ac.uk/bpsu accessed 12/02/2012).

Initial surveillance reports

Using the IPMSSG consensus definitions for classification of paediatric ADSs,(12) clinicians were asked to report children experiencing clinical neurological events consistent with a first episode ADS and confirmed with white matter changes (except in optic neuritis) on MRI (see Table 17).

Table 17: Summarised inclusion definitions for CNS Inflammatory Demyelinating Disease

Condition	Definition
Acute Disseminated Encephalo-myelitis (ADEM)	A polysymptomatic clinical event with acute/subacute onset that must include encephalopathy (behavioural change or altered consciousness). (2) MRI Brain shows multifocal lesions. If a new event occurs ≥3 months later and ≥1 month after completing steroid treatment, it is defined as: . Recurrent ADEM: recurrence of initial symptoms without involvement of new clinical areas. . Multiphasic ADEM: New event, but involving new anatomical areas of the CNS.
Clinically Isolated Syndrome (CIS)	A first acute-clinical episode of CNS symptoms which may either be monofocal or multifocal, but does not include encephalopathy (except in brainstem syndromes). The MRI will show white matter demyelination. These include: 1. Transverse myelitis (TM): weakness and/or numbness of both legs +/- arms, usually with maximal deficits 1 week after symptom onset supported by demyelination on MRI spine. 2. Optic Neuritis: Acute or subacute loss of vision and ≥1 of: relative afferent pupillary defect (unilateral cases), visual field deficit or scotoma, impaired colour vision, optic disc oedema, or abnormal visual evoked potentials. MRI is not necessary for diagnosis. 3. Other CIS: Brainstem, cerebellar, and/or hemispheric dysfunction, supported by demyelination on MRI.
Neuro-myelitis Optica (NMO)	Must have: i. Optic neuritis and ii. Acute myelitis. Must have: Spinal MRI lesion extends over three or more segments or iv. Aquaporin-4 antibody testing is positive. The brain MRI may be abnormal but must not meet Multiple Sclerosis MRI diagnosis criteria.
Exclusion criteria	1. Leukodystrophies (e.g., metachromatic leukodystrophy, adrenoleukodystrophy) or mitochondrial disease. 2. Proven CNS infection (e.g. viral encephalitis, bacterial meningitis, herpes simplex encephalitis, Lyme disease, HIV). 3. Radiation/chemotherapy associated white matter damage. 4. Condition fulfilling criteria for CNS connective tissue disease e.g. lupus, vasculitis. The sole presence of antibodies associated with CNS connective tissue or autoimmune diseases was not sufficient for exclusion.

Data Collection:

A condition specific targeted neurological history (using a check box questionnaire) took place at the time of first demyelinating event (see appendix). The event would be classified as either ADEM, CIS, or NMO (see). Data collected was broadly categorised to:

1. Basic demographic data (ethnicity, place of birth, residential areas)

2. Patient and family history of neuroinflammatory disorders (positive history of MS/ autoimmune disease)

3. Any precedent neurodisability or learning difficulties.

4. Demyelinating symptoms and signs (using tick box table, see attached questionnaire)

5. Presence of behavioural disturbance or encephalopathy (to distinguish ADEM from CIS)

6. Information which might predict the subsequent development of recurrent ADEM, multiphasic ADEM, or MS, like details of the anatomic distribution (optic nerve or spinal cord, monofocal or multifocal distribution), CSF findings, serological and neuroimaging results.

7. Treatment (eg, steroids, immunoglobulins, intensive care) given and duration of hospital stay.

8. Information as to whether the risk of future Multiple Sclerosis was given to the family.

9. In order to answer clinical questions and for our expert panel (which meets at 3 monthly intervals) to determine how to categorise cases, I will also ask for anonymous copies of the MRI.

MRI imaging review

MRI scans were reviewed blinded to clinical features jointly by MA and one of five neuroradiologists. A standardised proforma was completed utilising previously described nomenclature (see Table 18) (20, 77, 97). McDonald 2001 dissemination in space criteria (as recommended by the current IPMSSG criteria),(12, 192) McDonald 2010 dissemination in space and time (if a gadolinium enhancing scan was available) criteria and Verhey prognostic criteria were classified by MA according to the MRI variables and associated expert panel review.(22) Features of ADEM and CIS scans were compared. A single MRI protocol was not followed as this was a national population based study and collected data from established clinical practice in many centres. All MRI brain scans were performed on 1·5T scanners and had a minimum of a T1 weighted, and a T2 weighted or fluid-attenuated inversion recovery (FLAIR) sequence in two different planes. Additional sequences included gadolinium-enhanced T1, diffusion weighted and spine images. MRI slice thickness varied from 3–5 mm.

Autoantibody markers

The frequency of known results for antibodies to: AQP4; N-methyl-D-aspartate receptor (NMDAR); voltage-gated potassium-channel (VGKC) complex and myelin oligodendrocyte glycoprotein (MOG) were ascertained from routinely tested samples in the Oxford neroimmunology centre (one point national referral centre).

Table 18: MRI definitions used

MRI Lesion definitions:
- periventricular lesions: lesions in direct contact with the ventricular system (lateral or third);
- juxtacortical lesions: lesions in direct contact with the cortical gray matter with no intervening white matter;
- Infratentorial locations: brainstem and cerebellar lesions;
- cortical lesions: located within the cortical grey matter;
- corpus callosum: lesions perpendicular to the corpus callosum long axis;
- deep white matter: lesions in the supratentorial white matter which is not juxtacortical, corpus callosal or periventricular;
- large lesions: lesions in the white matter with a diameter larger than 2cm;
- deep grey nuclei lesions: thalamic and basal ganglia lesions which are located predominantly within grey matter;
- gadolinium enhancing lesion: hyperintense signal on T1-weighted contrast-enhanced imaging and corresponding to a T2 lesion;
- well defined and discrete lesions: clear lesions borders with an abrupt decrease in intensity of T2-weighted signal at the borderline between lesion and surrounding brain tissue;
- black hole: hypointense lesion(at least to grey matter) on T1-weighted image and is concordant with a hyperintense lesion on a T2-weighted image;
- spinal cord: lesion within the grey or white matter of the spinal cord; subclassified as whether equal or greater than 3 segments.

International Paediatric MS Study Group (IPMSSG) recommended McDonald 2001 criteria for dissemination in space (DIS):
Three out of four features are satisfied:
(1) nine or more T2 white matter lesions or one gadolinium-enhanced lesion;
(2) one juxtacortical lesion;
(3) three periventricular lesions;
(4) one infratentorial lesion.

McDonald 2010 DIS criteria are fulfilled if:
One or moreT2 lesion is present in two out of four areas:
(1) juxtacortical;
(2) periventricular;
(3) infratentorial;
(4) spinal cord (if the patient has a brainstem or spinal cord syndrome, symptomatic lesions are excluded from the criteria and do not contribute to the count).

McDonald 2010 dissemination in time (DIT) criteria can be fulfilled if:
a new T2 and or gadolinium-enhanced lesion is present on follow-up MRI irrespective of the timing of a baseline MRI, or if there is simultaneous presence of gadolinium-enhanced and non-enhanced lesions at any time (including at time of first scan).

Clinically Isolated Syndrome (CIS) Classifications:
Type 1 CIS: clinically monofocal, at least one asymptomatic MRI lesion
Type 2 CIS: clinically multifocal, at least one asymptomatic MRI lesion
Type 3 CIS: clinically monofocal, MRI may appear normal; no asymptomatic MRI lesions
Type 4 CIS: clinically multifocal, MRI may appear normal; no asymptomatic MRI lesions
Type 5 CIS: no clinical presentation to suggest demyelinating disease, but MRI is suggestive.

Expert panel classification and agreement for inclusion:

The co-investigators and members of the UK & Ireland Childhood CNS Inflammatory Demyelination Working Group met quarterly as an expert panel to review reported cases (at least four members present at each meeting). The expert panel consisted of eight paediatric neurologists with specialist expertise in ADS. Cases were presented by MA, and disagreements were resolved by consensus as per IPMSSG clinical criteria. Neuroradiologists were blinded to clinical features. MRI images (with neuroradiologist scoring) were used: to confirm presence of lesions consistent with inflammatory demyelination; to aid in exclusion of cases; classify according to MRI criteria; and to sub-classify CIS cases (see Table 18). (27)

Statistical Analysis

Descriptive statistics were used to summarise the key components of the dataset. Estimates of national incidence with confidence intervals (Byar's approximation of the exact Poisson) for the 13 month study was annualised using mid 2010 UK and 2010 Republic of Ireland population estimates.(196, 197) Mid 2009 population estimates by ethnicity for England and Wales were used to evaluate rates of childhood ADSs by ethnicity (198). A sensitivity analysis was conducted on a worst-case scenario that all reported cases with missing clinical histories were actually cases of ADSs to assess the potential impact on estimated incidence of ADSs. A two source case capture-recapture analysis was used to estimate missed cases of optic neuritis on the assumption of independence,(199) but did not carry out capture-recapture analysis for other ADSs, as referral networks mean that the assumption of independence was violated. The England 2010 index of multiple deprivation was used to derive the percentage of cases in England living in the 20% most deprived districts.(200) Parametric or non-parametric statistical tests (Kruskal Wallis tests) were used for continuous distributions as appropriate given normality and χ^2 or Fisher's exact tests for nominal data. Agreement

between reporters and the expert panel was measured using the Kappa statistic. Statistical analysis was performed using PASW Statistics for Windows version 17·0 (© SPSS, Inc., 2009, Chicago, IL, www.spss.com) and the openepi software (version 2·3·1, www.openepi.com).(201)

Ethical and regulatory approvals

The study protocol was approved by both the BPSU and BOSU executive committees. To comply with collection of minimal identifier information regulations without patient consent as in Section 251 of the NHS Act 2006, the study has approval from the National Information Governance Board's Ethics & Confidentiality Committee (ECC/BPSU 4-03 [FT1] /2009) and the UK Multicentre Research Ethics Committee (09/H1202/92). The study received research and development approval from the Birmingham Children's Hospital R&D department.

Risks, burdens, benefits and Confidentiality:

The Caldicott Principles and Data Protection act were be adhered to. Patient identifiable data was stored unlinked to the clinical data. A lay representative was assigned via the MS Society to ensure that patient and family views were appropriately sought throughout the study. Data handling was restricted to only those with direct involvement in the project. Data was secured in a lockable cabinet which is in a locked room. Minimal identifier data was collected (Table 19).

Table 19: Identifiers used and their justification

Identifier	Justification
NHS Number	To allow matching and deduplication between records and sources, and identifying cases to reporting clinicians, e.g. at follow-up.
Date of birth	For clinical analyses, and allow for anonymised linkage
Sex	For clinical analyses
District postcode	For epidemiological analyses
Ethnicity	For clinical-epidemiological analyses

2.3   Incidence

Card return rate, expert review and record linkage outcome

Card return rate was 94% from the BPSU and 78% from the BOSU (total of 47910 from 53235 [90%] cards returned including negative reports). A total of 222 positive notifications (197 BPSU and 25 BOSU) were received. There was insufficient information for review of 22 notifications (6 Scotland, 12 England & Wales, and 4 Ireland and Northern Ireland). In the remaining 200 (90%), 41 duplicate notifications were identified. Cases where the first event was outside the inclusion dates, September 2009 to September 2010 (n=16) were excluded. A further 18 cases were excluded by the expert panel (Figure 9). A total of 124/125 cases remaining had MRI scans (one isolated optic neuritis had no MRI scan, four transverse myelitis cases had MRI spine only).

Incidence of childhood CNS Inflammatory demyelination in the British Isles

The minimum incidence of first onset CNS inflammatory demyelination in children aged 1-15 years old in the British Isles is 9·83 per million children per year (95%CI 8·18-11·71). Incidence was highest in England and Wales (see Table 20). A sensitivity analysis on the assumption that all initial notifications where no further information was obtained were ADS showed no difference in incidence rates within countries in the British Isles.

Average monthly 4095 cards (2945 BPSU, 1150 BOSU) to clinicians every month for 13 months

(94% card return rate for BPSU- primary source & 78% for BOSU- secondary source
Overall 90%)

↓

200/222 (90%) information available for classification

↓

41 duplicates
(4 of excluded cases and 37 of included cases)

↓

159/200 remaining

↓

143/159 remaining   First

event outside

inclusion date

(n=16)

125 cases included   Excluded conditions (n=18)

Reported by:
Paediatrician- 22.4%
Paediatric Neurologist- 45.6
Ophthalmologist- 6.4%
Paediatrician & Paediatric Neurologist- 20.0%
Paediatrician or Paediatric Neurologist & Ophthalmologist- 5.6%

Cerebellitis (n=1);
H1N1 associated encephalitis (n=1);
Mumps associated encephalitis (n=1);
NMDAR antibody encephalitis (n=1);
Encephalitis (n=2);
Guillian Barre syndrome (n=2);
Chronic inflammatory demyelinating polyneuropathy (n=2);
Opsoclonus myoclonus syndrome (n=1);
Pneumococcal meningitisvasculitis (n=1);
Hypereosinophilic syndrome (n=1);
Cerebral vasculitis (n=1);
Metabolic syndrome (n=1);
Hodgkin's disease associated ON (n=1);
Post radiotherapy (n=1);
Post transplant lymphoproliferative disorder (n=1).

British Paediatric Surveillance Unit (BPSU); British Ophthalmological Surveillance Unit (BOSU); N-Methyl-D-aspartate (NMDA); Chronic inflammatory demyelinating polyneuropathy (CIDP); Post transplant lymphoproliferative disorder (PTLD).

Table 20: Incidence of childhood Acquired demyelinating syndromes by country, sensitivity analysis and ethnic group in England and Wales

CONFIRMED CASES						
Region	Number	Percent	Pop. 2010 1-15 years (per thousands) or %	Incidence per annum per million	95% CI lower	95% CI upper
England, Wales & Channel Islands	117	93.6	9636	11.2	9.27	13.4
Scotland	3	2.4	853	3.25	0.65	9.49
Ireland & Northern Ireland	5	4.0	1254	3.68	1.19	8.59
Total	125	100.0	11743	9.83	8.18	11.71
SENSITIVITY ANALYSIS ASSUMING ALL REPORTS WITH MISSING INFORMATION ARE CASES						
England, Wales & Channel Islands	129	87.8	9636	12.36	10.32	12.68
Scotland	9	6.1	853	9.74	4.44	18.5
Ireland & Northern Ireland	9	6.1	1254	6.63	3.0	12.6
Total	147	100.0	11743	11.6	9.76	13.6
INCIDENCE BY ETHNICITY IN ENGLAND & WALES						
White	93	80.17%	83.93%	10.62	8.57	13.00
South Asian	11	9.48%	7.30%	14.43	7.20	25.83
Black	7	6.03%	3.31%	20.25	8.12	41.73
Chinese, mixed and other	5	4.31%	5.46%	8.78	8.28	20.27
Total	116	116	100%			

Capture-recapture analysis

Capture-recapture analysis (Table 21) for optic neuritis cases (n=31) assuming that BPSU and BOSU were independent sources of cases estimated the total population to be 47 (95% CI 30-55).

Table 21: Two source case capture-recapture(199):

		Cases ascertained via BOSU		
		Yes	No	Total
Cases ascertained	Yes	7 (c)	16	23 (a)
via BPSU	No	8	(d)	b – c + d
		15 (b)	a- c +d	N=estimated total

Assumption: probability of ascertainment from both sources equal where:

a= cases ascertained by primary source

b= cases ascertained by secondary source

c= cases ascertained by both sources

d= cases not ascertained by either source (N- a -b + c)

N= [(a+1) x (b+1)/ (c+1)] -1= 47 (95% CI 30-55)

2.4   Demographic & Clinical Features of the ADS

Demographic characteristics

Median age was 10·0 years (range=1·3-15·9) and 51·2% (64) of cases were female (see Table 22). The median age for males was 8·9 years (IQR 5·0-13·5) and for females was 11·4 years (IQR 6·8-14·4) (p=0·046 Kruskal Wallis test). The female to male ratio in children younger than ten years (n=62) was 0·72:1 and in children older than 10 years old (n=63) was 1·52:1. White children comprised 81% of the total cohort. Higher incidence rates of ADS in children of South Asian and black ethnicity in England and Wales compared to white children were not statistically significant (see Table 20). A total of 34% of the cases in England lived in the most 20% deprived districts.

Table 22: Clinical, demographic, and phenotypic classification of the childhood Acquired demyelinating syndromes

		Expert classification				
			CIS (n=83)			
		ADEM (n=40)	ON (n=31)	TM (n=26)	Other CIS (n=26)	NMO (n=2)
Age At Presentation: median (IQR)		5.3 (3.6-7.0)	11.8 (9.0-13.9)	12.6 (9.3-14.0)	14.0 (9.5-14.5)	n/a 6.4, 14.8 years
Sex (n=125)	**Male: Female (% female) 61: 64 (51%)**	24:16 (40%)	15:16 (52%) 37:46 (55%)	11:15 (58%)	11:15 (58%)	0:2 (100%)
Ethnicity (n=124/125)	**White (n=101)**	36 (90%)	21 (68%)	22 (85%)	21 (81%)	1 (50%)
	Asian (n=11)	3	4	2	1	1
	Black (n=7)	1	3	1	2	0
	Chinese, mixed, other (n=5)	0	3	1	1	0
Clinical:	MRI:					
Monofocal	≥ 1 asymptomatic lesion		7 (23%)	9 (35%)	4 (15%)	
	no asymptomatic		24	17	3 (12%)	
Multifocal	≥ 1 asymptomatic		0	0	16 (62%)	
	no asymptomatic		0	0	2 (8%)	
Radiologically isolated			n/a	n/a	1	
Spinal lesion(s) present: n (% ≥3 lesions)		8/12 (100%)	1/8 (0)	26/26 (62%)	4/9 (75%)	2/2 (100%)
Death		1/40 (2.5%)	0	0	0	0
Seizures		8/40 (20%)	0	0	0	0
Optic neuritis: Unilateral: bilateral (% bilateral)		0:3 (100%)	22:9 (29%)	0:0	0:1	1:1 (50%)
Cerebellar signs: n (%)		18 (45%)	0	0	11 (42%)	0
Brain stem signs: n (%)		11 (28%)	0	1	13 (50%)	0
Pyramidal signs: n (%)		24 (60%)	0	0	10 (38%)	0
Intensive Care Unit admissions; *n=12 (10%)*		8 (20%)	0/31 (0%)	3/26 (12%)	1/26 (4%)	0/2
Plasma exchange; *n=4 (3%)*		2 (5%)	0/31	2/26 (8%)	0/26	0/2
Intravenous Corticosteroids		37/40 (93%)	23/31 (74%)	25/26 (96%)	18/26 (69%)	2/2 (100%)
Oral steroids		27/40 (68%)	21/31 (67%)	16/26 (62%)	11/26 (42%)	2/2 (100%)
Intravenous Immunoglobulin		6/40 (15%)	0	7/26 (27%)	1/26 (4%)	0

Results of expert panel review and clinical classification

Childhood ADS disorders were classified as CIS in 66·4%, ADEM in 32·0% and neuromyelitis optic (NMO) in 1·6%. Of the CIS cases, optic neuritis (ON) represented 37·4%, transverse myelitis (TM) 31·3% and other clinically isolated syndromes 31·3% (see Table 22). The majority (70%) of the other CIS cases were polysymptomatic. Children with ADEM were more likely to be younger than cases presenting with CIS ($p<0·001$) (see Figure 10). The risk ratio for CIS in females compared to males was 1·46 (95% CI 1·17, 1·83). The expert panel reclassified (blinded to initial diagnosis) a total of 15 out of the 125 cases (12%): ADEM to CIS (n=11); Other CIS to TM (n=3); TM to other CIS (n=1). The overall level of agreement between reporters and the expert panel was good (Kappa 0·838 [95 % CI 0·761-0·914]).

Figure 10: Childhood CNS inflammatory diseases phenotype by age (younger and greater than 10 years old) and sex
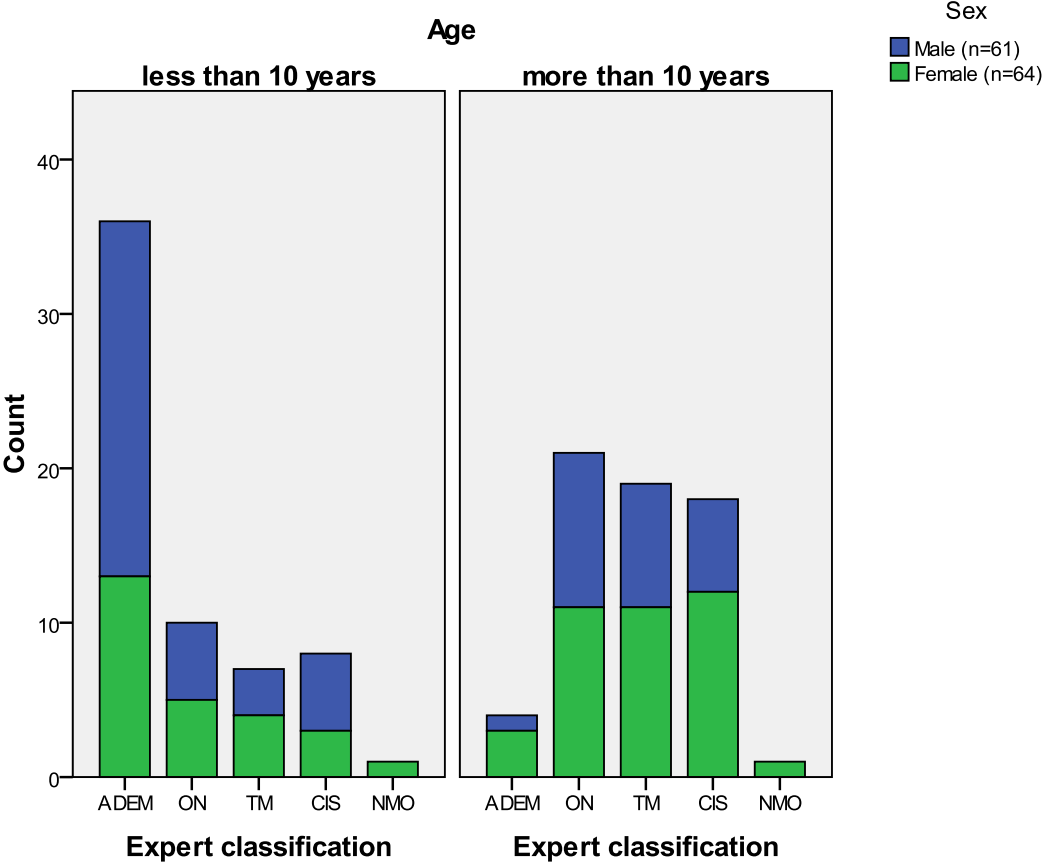
Deaths

Clinicians reported three deaths in the initial hospital admission, one in a child with ADEM and two in cases which proved not to have ADS (post transplant lymphoproliferative disorder and hypereosinophilic syndrome).

2.5   MRI features

More CIS cases fulfilled MRI McDonald 2010 dissemination in space criteria (42%) compared to the 2001 criteria (28%; see Table 23). Of the CIS cases which had contrast enhanced scans (n=38), 10 cases (26%) fulfilled McDonald 2010 space and time criteria for MS diagnosis. Verhey MRI prognostic criteria for identifying childhood ADS cases at high risk of MS (presence of one T1 hypointense and one periventricular lesion) were fulfilled in 11/78 (14%) CIS cases compared to 1/40 (2·5%) ADEM cases. A total of 19/78 (24%) CIS cases fulfilled either Verhey prognostic criteria or McDonald 2010 MS space and time criteria for MS (8/10 cases which fulfilling McDonald 2010 space and time criteria did not fulfil Verhey criteria, whilst 3/5 fulfilling Verhey criteria did not fulfil McDonald criteria).

ADEM cases compared to CIS cases with abnormal MRI (see Table 24) were more likely to have more: deep grey nuclei ($p<0·001$); large white matter ($p<0·001$); and cortical grey matter ($p=0·001$) high T2 signal lesions. CIS scans were more likely to have more: periventricular ($p<0·001$); deep white matter ($p=0·003$); corpus callosum ($p=0·001$); well defined and discrete high T2 signal lesions ($p<0·001$) and black holes ($p=0·008$). The number of total high T2 signal, enhancing, infratentorial, juxtacortical and spinal lesions did not differentiate between CIS and ADEM patients (see Table 24). Of the ON and TM cases (monofocal CIS) 23% and 35% had one or more high T2 signal brain lesion respectively.

Table 23: MRI criteria fulfilled

	Expert classification		
	CIS (n=83)		
	ON (n=31)	TM (n=26)	Other CIS (n=26)
McDonald 2001 space criteria	4/30	5/22	13/26
	22/78 (28%)		
McDonald 2010 space criteria	5/30	8/22	20/26
	33/78 (42%)		
McDonald 2010 time criteria (Gadolinium given scans)	0/12	3/11	7/15
	10/38 (26%)		
Meets McDonald MRI criteria for MS on initial presentation (dissemination in space and time)	10/38 (26%)		
Verhey or McDonald 2010 MS criteria present	19/78 (24%)		

Table 24: Comparison of MRI features in Clinically Isolated Syndrome (CIS) cases with abnormal MRI scans (n=41) and Acute Disseminated Encephalomyelitis (ADEM) cases (n=40)

	Lesions (n)	CIS	ADEM
T2 total lesions	1-4 lesions	12	17 (43%)
	5-10 lesions	8	7
P=0.084	>10 lesions	21 (51%)	16
Gadolinium enhancing lesions	0 lesions	12 (52%)	13 (72%)
p=0.385	1-2 lesions	7	2
	>2 lesions	4	3
Periventricular lesions	0 lesions	13	31 (78%)
	1-4 lesions	11	5
p<0.001	>4 lesions	17 (41%)	4
Juxtacortical lesions	0 lesions	14	16 (40%)
	1-4 lesions	9	10
P=0.42	>4 lesions	18 (44%)	14
Deep white matter lesions	0 lesions	11	20 (40%)
	1-4 lesions	7	11
p=0.003	>4 lesions	23 (56%)	9
Cerebellar lesions	0 lesions	27 (66%)	23 (58%)
	1-2 lesions	10	15
p=0.053	>2 lesions	4	2
Brainstem lesions	0 lesions	20 (49%)	18 (45%)
	1-2 lesions	16	19
p=0.931	>2 lesions	5	3
Corpus Callosum lesions	0 lesions	24 (59%)	37 (93%)
	1-2 lesions	12	1
p=0.001	>2 lesions	5	2
Thalamic/ basal ganglia	0 lesions	39	16
p<0.001	1-2 lesions	1	18
	>2 lesions	1	6
Black Holes p=0.008		11/41(27%)	2/40 (5%)
Well Demarcated (p<0.001)		30/41(73%)	11/40 (28%)
Large lesions present (p<0.001)		26/41(63%)	8/40 (20%)
Cortical grey lesions	0 lesions	39 (95%)	26
p=0.001	≥1 lesion	2	14 (35%)
Spinal lesions (p=0.851)		13/20 (65%)	8/12 (67%)
Spinal >3segments (p=0.13)		9/13 (69%)	8/8 (100%)

2.6   Investigative & Immunological Features

Investigative features

Children with ADEM more commonly had CSF lymphocytosis (p=0·005) and less commonly CSF positive oligoclonal bands (p=0·011) compared to those with CIS (see Table 26: Investigative features). One ADEM case was reported as having the common missense mutation (c.1880CT, p.Thr585Met) of the Ran Binding Protein 2 (RANBP2) gene previously reported in recurrent or familial acute necrotising encephalopathy.(134) Of those tested for the aquaporin-4 antibody (n=52), none of the ADEM, TM, and other CIS cases tested positive while one child with optic neuritis and both NMO patients tested positive.

Autoantibody markers

The following were positive (total 8/63, 13%) for antibodies against: 3/52 AQP4 (6%), 2/17 NMDAR (12%), 1/12 VGKC-complex (8%) and 2/8 MOG (25%) (Table 25). Of the AQP4 positive: one had unilateral optic neuritis (ON) and longitudinal extensive transverse myelitis (LETM) with normal brain MRI; one had bilateral ON and LETM with an acute disseminated encephalomyelitis (ADEM) like MRI; and one had isolated ON with poor visual recovery (normal brain and spine MRI). Of the NMDAR positive: both had severe ADEM presentations and bilateral external capsule involvement and either deep grey nuclei or cortical involvement. The VGKC positive case had ADEM like presentation with bilateral basal ganglia involvement. Both MOG positive cases had ADEM presentation with MRI showing asymmetric and diffuse cortical grey, white matter, deep grey nuclei, and infratentorial lesions.

Table 25: Autoantibodies in ADS

	Expert classification				
		CIS (n=83)			
	ADEM (n=40)	ON (n=31)	TM (n=26)	Other CIS (n=26)	NMO (n=2)
AQP4 antibody	0/5	1/18	0/20	0/7	2/2
MOG antibody	2/2	0/2	0/2	0/2	0/0
NMDAR antibody	2/9	0/3	0/3	0/2	0/0
VGKC antibody	1/7	0/1	0/2	0/2	0/0

Cerebrospinal Fluid (CSF); Aquaporin-4 antibody (AQP4); N-methyl-D-aspartate receptor (NMDAR); voltage-gated potassium-channel (VGKC) complex; myelin oligodendrocyte glycoprotein (MOG); Ran Binding Protein 2 gene (RANBP2).

Table 26: Investigative features

Cerebrospinal fluid (CSF) Result	Expert classification				
		CIS (n=83)			
	ADEM (n=40)	ON (n=31)	TM (n=26)	Other CIS (n=26)	NMO (n=2)
CSF Oligoclonal bands	2/20 (10%)	6/17 (35%)	6/19 (32%)	10/15 (67%)	0/1 (0%)
CSF WBC ≥5x 10^6/L	21/36 (58%)	3/17 (18%)	8/20 (40%)	8/21 (38%)	0/2 (0%)
CSF protein median (IQR)	0.38 (0.25-0.58) n=28	0.26 (0.23-0.35) n=17	0.36 (0.26-0.52) n=19	0.29 (0.21-0.36) n=17	0.29 n=2

2.7   Differential Diagnosis

Excluded cases

On review 19 cases were considered not to have 1st episode demyelination. Table 27 details the excluded cases by final expert panel diagnosis against how they were reported to the study. The final column also details comments on why the diagnosis was changed.

Table 27: Details of excluded cases

Case number / ID	Expert panel diagnosis	Reported by	Country	Reported as	Age/sex	Comments i.e. why change of diagnosis
1. 1001/10	Cerebellitis	Paediatrician	England	CIS	7yr, male	Cerebellar symptoms limited to cortical grey matter on MRI
2. 0911/06	H1N1 associated encephalitis	Paediatrician & Paediatric Neurologist	Scotland	ADEM	1yr, female	Normal MRI brain scan H1N1 positive
3. 1004/17	Mumps associated encephalitis	Paediatrician	England	ADEM	15yr, male	Mumps positive Cortical brain MRI changes
4. 1007/05	NMDAR antibody encephalitis	Paediatrician	England	ADEM	15yr, female	Mycoplasma positive/ NMDAR positive MRI brain normal
5. 1003/30	Encephalitis	Paediatrician	England	ADEM	5 yr, female	MRI brain normal
6. 1008/10	Encephalitis	Paediatric Neurologist	England	ADEM	15yr, Female	MRI brain normal
7. 0910/05	Guillain-Barre syndrome	Paediatrician	England	TM	9yr, male	MRI spine normal Clinical and electrophysiological findings of peripheral demyelination
8. 1001/03	Guillain-Barre syndrome	Paediatrician	England	TM	11 yr, male	MRI spine normal Clinical and electrophysiological findings of peripheral demyelination
9. 0909/14	Chronic inflammatory demyelinating polyneuropathy	Paediatrician	England	TM	14yr, female	Abnormal nerve conduction studies. Also has known Systemic Lupus Erythematosus
10 1007/07	Chronic inflammatory demyelinating polyneuropathy	Paediatrician	England	TM	4yr, female	Abnormal nerve conduction studies Normal MRI spine

Table 27: Details of excluded cases *continued..*						
Case number / ID	**Expert panel diagnosis**	**Reported by**	**Country**	**Reported as**	**Age/sex**	**Comments i.e. why change of diagnosis**
11 1009/03	Opsoclonus myoclonus syndrome	Paediatrician	England	ADEM	1yr, male	Normal MRI brain Clinical features of Opsoclonus Myoclonus Syndrome
12 0911/11	Pneumococcal meningitis/ vasculitis	Paediatric Neurologist	England	ADEM	2yr, Male	Vasculitic lesions on MRI brain. CSF positive for pneumococcus
13 1002/02	Hypereosinophilic syndrome	Paediatrician	England	CIS	14ys, female	Eosinophilia, and clinical features of hypereosinophilic syndrome . MRI brain: numerous small deep white matter lesions.
14 1009/02	Cerebral vasculitis	Paediatrician	England	ADEM	12yr, male	Localised cortical inflammation. Ophthalmic zoster.
15 1008/12	Metabolic syndrome	Paediatrician	England	ADEM	2yr, male	Referred to tertiary metabolic centre. Demyelination ruled out.
16 ON 0910/03	Hodgkin's disease associated ON	Ophthalmologist	England	ON	12yr, female	Hodgkin's disease related relapse
17 0909/02	Post radiotherapy	Paediatrician	Scotland	ADEM	5yr, female	Post radiotherapy disease for medulloblastoma. MRI: cortical diffuse cerebellar lesion.
18 0911/01	Post transplant lympho-proliferative disorder	Paediatric Neurologist	England	ADEM	2yr, male	Immunosuppression Post bowel transplant.

2.8   Treatment

The majority (89%) received either intravenous corticosteroids (84%) and/or oral prednisolone in the first instance (see Table 28). Children with ADEM were more likely to require intensive care unit (ICU) admission, and four children (2 ADEM and 2 TM) received plasma exchange. Intravenous immunoglobulin was administered to 11% of the cohort.

Table 28: Treatment of ADS

	Expert classification				
		CIS (n=83)			
	ADEM (n=40)	ON (n=31)	TM (n=26)	Other CIS (n=26)	NMO (n=2)
Intensive Care Unit admissions; *n=12 (10%)*	8 (20%)	0/31 (0%)	3/26 (12%)	1/26 (4%)	0/2
Plasma exchange; *n=4 (3%)*	2 (5%)	0/31	2/26 (8%)	0/26	0/2
Intravenous Corticosteroids	37/40 (93%)	23/31 (74%)	25/26 (96%)	18/26 (69%)	2/2 (100%)
Oral steroids	27/40 (68%)	21/31 (67%)	16/26 (62%)	11/26 (42%)	2/2 (100%)
Intravenous Immunoglobulin	6/40 (15%)	0	7/26 (27%)	1/26 (4%)	0

2.9   Discussion

Incidence of childhood ADS

The minimum incidence of first onset childhood ADS in the British Isles is 9·83 per million (95% CI 8·18-11·71) children per year aged 1-15 years. This is the highest reported incidence of childhood ADSs from a prospective childhood surveillance study. Published studies reporting on the incidence of childhood ADSs (summarised in Table 5) included one retrospective analysis of a patient database, a multicentre retrospective study, a single centre prospective study, and two prospective population based surveillance studies. This study is a novel large multinational interdisciplinary epidemiological study which uses multiple sources and two well established active surveillance units. Unique to this surveillance study is integrated detailed review of MRI images and investigative features and combines this with the robust application of criteria by an expert panel (for inclusion, exclusion and differential diagnoses).

To date, there have been two surveillance studies studying ADSs. A Canadian surveillance study (2004-2007) estimated the incidence of childhood ADSs to be 9·0 per million,(32) with 22% classified as ADEM and 78% as CIS. This study however used a single surveillance system with a card return rate of 80%; did not have MRI available or have expert panel review; included adolescents up to the age of 18; did not include neuromyelitis optica; and commenced before IPMSSG definitions were published. An earlier surveillance study from Germany (1997-1999) estimated the incidence of MS in children <16 years as 3·0 per million children, and that of ADEM as only 0·7 per year per million children.(31) This study also used only one source with ascertainment from paediatric departments; did not have MRI

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available or expert review; and did not include other ADSs. Diagnosis of MS depends on clinical definitions and MRI criteria used. Hence, reliable ascertainment requires expert review as in the study reported here.

Limitations

This study is not without limitations. As with other epidemiological studies, some cases may not have been reported or have had sub-clinical presentations, and it is plausible that children in our study who met criteria for MS at first clinical presentation may have had previous symptoms not identified as ADS. This was addressed as far as was possible by using clear consensus case definitions and multiple sources of case ascertainment. A capture-recapture analysis estimated that a possible 16 optic neuritis cases were missed out of a potential 47, although this relies on strong assumptions of complete independence that may not hold in practice. It suggests however that actual incidence may be higher than reported.

Demographics and clinical-radiological phenotype

Previous MS studies have shown that adolescent females are over-represented compared to males with ratios of up to 3:1 (5-7). A recent retrospective study from the USA showed the incidence of childhood ADSs and MS to be higher in black children compared with white and Hispanic children(33). While non-white ethnic groups were over represented in our study, this did not reach statistical significance but this still contrasts with the adult MS population where white ethnic groups are over-represented. Adult MS studies have also shown a consistent increase in female MS incidence, compared to males, as well as a higher risk ratio of females developing CIS,(8) the first presentation of MS. Our study is the first to show that in childhood ADSs, sex ratios also varied with age, with more males in younger age groups

and more females in the older age groups (F:M ratio of 1·52:1 in children over 10 years). Children older than 10 years more often had CIS compared to those less than 10 years of age who presented more often with ADEM. A Japanese retrospective multicenter study showed the male to female ratio of ADEM to be 2·3:1, and that ADEM was three times more common than MS.(36) These observations regarding the demographics of childhood ADSs support the hypothesis that gene-environment interactions (which might include vitamin D) may indeed be acting as early as in childhood.

Our study shows that CIS occurs more often than ADEM (ratio 2·1:1) in children and also confirms a previous report that ADEM can be a severe disease with one death and one in five requiring intensive care admission.(202) I found that 43% of CIS patients had one or more asymptomatic brain lesion. Previous studies have shown that children with CIS with abnormal brain scans are at a higher risk of relapse than those with ADEM (21, 23).

MRI features

This is the first study which has applied the newly revised MS 2010 McDonald diagnostic criteria in a population based series. A total of 26% of CIS cases who had gadolinium given scans (n=38) fulfilled McDonald 2010 MRI criteria for MS at onset (space and time), hence a minimum 12% of CIS patients met McDonald 2010 MS diagnostic criteria at diagnosis. In addition 24% of CIS cases fulfilled either McDonald 2010 or Verhey criteria which are thought to indicate higher risk of MS, although both the McDonald criteria and the Verhey model require further validation in prospective multinational cohorts. This is particularly the case as in this study 8/10 of cases fulfilling McDonald 2010 MS criteria did not meet the criteria from Verhey's predictive model. Also it is of interest that a number of MRI measures

significant helped differentiate ADEM from CIS cases. For example ADEM cases compared to CIS had more: deep grey nuclei; and cortical grey matter; high T2 signal lesions. CIS had more: periventricular; deep white matter; corpus callosum; and black holes. I have previously shown that 61% of children eventually diagnosed with MS and who had contrast enhanced scans at ADS onset fulfilled McDonald 2010 MS criteria at first scan.(7) Not all children in this study had spinal imaging and contrast administered, and MRI sequence variation could have affected the sensitivity of MRI.

Investigative features

CSF lymphocytosis and negative CSF oligoclonal bands were significantly associated with an ADEM diagnosis, in contrast to a previous study (26).

Autoantibody markers

CNS inflammatory demyelination (ADS) results from activation of antigen-specific T cells together with a humoral response. Potentially pathogenic CNS directed antibodies like myelin oligodendrocyte glycoprotein (MOG) are increasingly being reported in the context of adult (203) and childhood Acquired demyelinating syndromes,(204-206) implicating a role for B cell and antibody mediated mechanisms in ADS. In neuromyelitis optica (NMO), antibody to aquaporin 4 (AQP4) is a specific disease biomarker (207).

In addition to AQP4, other circulating CNS directed autoantibodies, are associated with childhood ADS. In this study 14% of cases (other than NMO) tested were positive for these antibodies. As the presence of these self directed autoantibodies may simply reflect the secondary upregulation of the immune system, future systematic biomarker studies are required to evaluate the pathogenic role of these auto-antigens, or if they may be potential biomarkers for a subtype specific ADS.

Genetic insights

It is of interest that one case was reported as positive for the common mutation in the RANBP2 gene, which has been recently described in familial or recurrent acute necrotizing encephalopathy (ANE) (134). With the increasing recognition of the overlap between the MRI and clinical features of ADEM and ANE, and further reports of other genetically predetermined encephalopathies,(208) this potential novel group of genetic determinant(s) of encephalopathy in demyelination requires further exploration.

Differential Diagnosis

The differential diagnoses for ADEM and MS are recognised as challenging dilemmas when presenting to clinicians and need to be carefully considered (27, 28). The differential in the study included: other CNS inflammatory causes (cerebellitis); infections (H1N1 encephalitis, mumps encephalitis, other viral encephalitis, pneumococcal meningitis); auto-antibody mediated diseases (Anti-N-methyl-D-aspartate receptor encephalitis); other CNS autoimmune disorders (Opsoclonus myoclonus syndrome); peripheral demyelinating diseases (Guillian Barre syndrome, and chronic inflammatory demyelinating polyneuropathy); cerebral vasculitis; peripheral demyelinating diseases (Guillian Barre syndrome, and chronic inflammatory demyelinating polyneuropathy); tumour related events (Hodgkin's disease associated optic neuritis, post radiotherapy, post transplant lympho-proliferative disorder); metabolic syndromes; haematological (hypereosinophilic syndrome). Out of the 18 cases incorrectly reported; 11 (61%) were reported as ADEM; 4 (22%) were reported as TM; and 3 were other CIS cases. This indicates that more severe presentations including those with encephalopathy are most likely to be misdiagnosed which has implications for NHS clinical practice and indeed internationally. Of note is that 14 of the 18

cases initially presented to general paediatricians (who reported the cases) who are likely to have relatively little experience of recognising managing these rare neurological diseases—this raises the issue of continuous education and increasing awareness in rare neurological presentations amongst practicing generalists. Importantly two patients not classified as having ADS died, raising the possibility that early recognition may have changed management and outcome. In children who have received immunosuppression, chemotherapy or radiotherapy and present with polyfocal neurological symptoms and multiple white matter lesions; tumour related events should be considered.

The study has highlighted a number of other key management issues Cerebellitis should be considered when a patient presents with cerebellar symptoms limited to cortical grey matter on MRI. It is important to recognise cerebellitis as hydrocephalus is a well recognised and treatable complication (209). Normal MRI brain scans or those showing just cortical grey matter changes in the context of children presenting with encephalopathy and polyfocal neurological symptoms/signs, should raise the suspicion of infective or immune mediated CNS disease. In children presenting with bilateral lower limb weakness, and a normal MRI spine- abnormal nerve conduction studies will help confirm clinical findings of peripheral demyelinating disease. Children presenting with encephalopathy, polyfocal neurological symptoms, and MRI brain showing multiple widespread grey and white matter punctuate ischaemic/ vasculitic lesions should point towards infectious meningitis (with CSF examination providing further support).

The management of paediatric acquired demyelinating syndromes indeed are also relatively under-recognised amongst practising paediatric neurologists, hence the set up of the UK

childhood inflammatory demyelinating disease working group (I am one of founding members) and the international paediatric multiple sclerosis study group (12, 210). The surveillance study has highlighted a number of differential diagnostic features which may be incorporated into national clinical guidelines or education programmes for paediatricians and neurologists.

Treatment

There are no controlled trials for the treatment of ADS in childhood. Most recommendations are mainly extrapolated from case series or data from clinical trials for the treatment of exacerbations of adult MS (41, 50, 158). Children are usually treated with high dose intravenous steroids for 3-5 days to attenuate inflammation .In this study, the majority (84%) received intravenous corticosteroids for the acute treatment of ADS. Subsequent oral steroid taper with a duration of 2–6 weeks is usually recommended for ADEM (5, 15, 211). Despite this, in this study only 68% of ADEM cases received an oral steroid taper. In children who do not respond to steroids, intravenous immunoglobulin is often used, although the data to support this is limited to small case series and single case reports (5). Intravenous immunoglobulin was administered to 11% of the cohort, with 13 of the 14 being given to children with ADEM or TM, representing the more severe ADS presentations. In cases of severe or life-threatening acute demyelination, plasma exchange should be considered. Plasmapharesis is increasingly used as rescue therapy based on its efficacy in a small randomised controlled trial in adults with acute CNS demyelination (160). Only four children (2 ADEM and 2 TM) received plasma exchange in this study, despite 12 having a severe disease as evidenced by needing an intensive care unit admission. The variable treatments

given at first ADS presentation, highlights the need for future clinical trials for acute ADS therapies and establishing guidelines for clinical practice.

Conclusions

In this study I report the highest surveillance incidence rates of childhood ADS to date and show that children of non-white ethnicity are not underrepresented as expected from adult MS studies. This study is the first to show that in childhood ADS, sex ratios varied with age, with more females in older age groups. The observations regarding the demographics of childhood ADS (changing sex ratios with age, and increased over representation of non-white ethnicity) support the hypothesis that changing environmental risk factors for MS may indeed be operating in childhood, hence having implications for future preventative studies (such as use of Vitamin D supplementation).

This is also the first study which has applied the newly revised MS 2010 Macdonald diagnostic criteria in a prospective population based series. I also showed that a minimum 24% of first onset met criteria for being at high risk of MS diagnosis at first presentation and hence were potentially eligible for early disease modifying treatment. The variable treatments given at first ADS presentation also highlights the need for future clinical trials for acute ADS therapies.

The potential to diagnose MS at disease onset has implications for MRI protocols for children with suspected ADS, and individual patient treatment decisions. This may be particularly

important as new MS drugs are emerging with reported better efficacy in adults than current injectables, and the simultaneous requirement for new drugs to undergo testing in children with the aim of ensuring robust evidence to support authorisation by regulatory agencies. To date, eight new MS drugs have been recommended for a Paediatric Investigation Plan,(212) hence earlier diagnosis may increase the eligible clinical trial population. Prognostic and outcome data are needed to inform these decisions. In the next chapter I will discuss a prospective one year follow up of this patient cohort is under way and a further multicentre cohort study which will yield prognostic information for early diagnosis of MS in children.

CHAPTER 3 OUTCOMES IN ADS

There is limited data limited data on the natural history and prognostic features of acquired demyelinating syndromes (ADS). In this chapter I describe a series of longitudinal retrospective case series to address the prognosis following a first episode of ADS, and also describe the one year outcomes from the national prospective surveillance study. In the chapter I aim to present a number of childhood ADS conditions and prognostic features, these are:

- Chapter 3.1: a multicentre longitudinal retrospective case series including 44 children with childhood optic neuritis;

- Chapter 3.2: a multicentre longitudinal retrospective case series including 44 children a population based study involving intensive care units (n=27);

- Chapter 3.3: a retrospective analysis of 38 childhood onset MS cases from three UK demyelination clinics was conducted;

- Chapter 3.4: a historical neuromyelitis optica (NMO) longitudinal cohort (n=22) with known aquaporin-4 antibody (AQP4-ab) status and compare it to a contemporary incident national cohort sample;

- Chapter 3.5: early outcomes and prognostic factors in a one year follow up of the national surveillance study,

3.1 Childhood optic neuritis clinical features and outcome

INTRODUCTION

Childhood optic neuritis (ON) due to demyelination is a potentially treatable condition that may lead to visual impairment. A recent Canadian surveillance study showed an incidence of 0.2 per 100,000 children (32). However, incidence rates are likely to be geographically different and more studies are needed. Isolated ON may also be the first manifestation of Multiple Sclerosis (MS) or Neuromyelitis Optica (NMO). The natural history of childhood optic neuritis (ON) remains relatively unreported. Case series reported in the literature have tended to be single centre studies, not included NMO as an outcome and some have included cases of polysymptomatic clinically isolated syndromes (CIS) at presentation (54-59). I reviewed isolated first episode childhood ON cases in three tertiary UK centres to evaluate clinical features and outcome. A secondary aim was to inform the design of a prospective national epidemiological surveillance study.

METHODS

Computerised databases were searched for consecutive cases to indentify ON cases between 1st January 2002 and 31st March 2008. The age at presentation was limited from 1 month to less than 16 years of age. A text-based departmental database of patients seen in the paediatric neurology and ophthalmology departments was searched using the terms "optic neuritis." Searches were conducted in three UK Children's Hospitals. Patients' notes were retrospectively analysed. I included cases with acute or subacute visual loss and one or more of the following: relative afferent pupillary defect (RAPD) in the affected eye in

unilateral cases, visual field deficit or scotoma, impaired colour vision, optic disc oedema, or abnormal visual evoked potentials (VEPs).

I excluded cases with; other neurological findings; concurrent acute disseminated encephalomyelitis (ADEM); other causative aetiology; or previous CNS inflammatory demyelinating episodes. Conditions excluded were anterior ischemic optic neuropathy; neuroretinitis; compressive or infiltrative optic neuropathies; Leber's hereditary optic neuropathy.

Any pre-existing ophthalmic conditions that had affected visual acuity were noted. At least two researchers in each centre carried out the search and decided on inclusion, and in case of disagreement the first author was consulted. The primary outcome was visual acuity at recovery, and the secondary outcome was MS or NMO diagnosis on follow up. A 'positive MRI' was defined as showing one or more brain T2 hyperintense lesions. International Paediatric MS Study group consensus definitions(12) were used for defining MS and other CNS demyelinating conditions.

An excel spreadsheet was designed to collect and record anonymised data in the three centres. Descriptive data are presented. Statistical analysis utilised life-table analysis by the Kaplan-Meier method performed using SPSS (version 17.0) software.

RESULTS

Presenting features

Searches indentified a total of 44 consecutive cases that were eligible for inclusion. Ages ranged from 2.0 years to 15.8 years with a median of 10.9 years (interquartile range 9.0-13 years). The female: male ratio was 1.8 (p= 0.07). ON was unilateral in 43% and bilateral in

57%. Maximal visual deficit at presentation was severe (a snellen equivalent of <6/60 [LogMAR 1.00]) in 77% of cases.

Outcome

Cases were followed up for 2 months to up to 6 years (mean 1 yr, 10months, median 1 yr). Visual recovery (to pre-existing visual acuity if known, or a snellen equivalent of 6/9 or better[LogMAR 0.18]) occurred in 70% (41/59 eyes). Data on visual recovery was not available for 10 eyes. On follow up, 32% were diagnosed with MS (11/44) or NMO (3/44). Cumulative probability of cases developing MS or NMO (*see* Figure 11) by 2 years after ON onset was 0.45 (95% CI 0.25-0.65). Gender, age (younger or older than ten years of age), unilateral/bilateral ON, and visual acuity severity did not predict MS development. Relapsing ON (*see* Figure 12) was a strong predictor for the development of MS or NMO (logrank p<0.001).

Figure 11: Kaplan-Meier Curve showing cumulative probability of MS or NMO diagnosis after ON onset
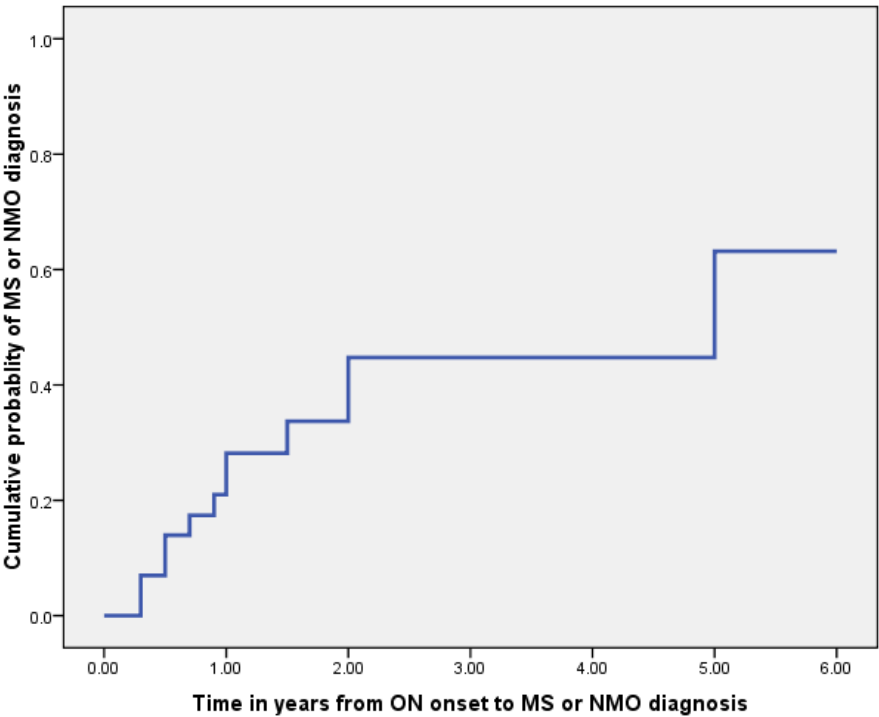
Figure 12: Kaplan-Meier Curves showing cumulative probability of MS or NMO diagnosis after ON onset with relapsing ON
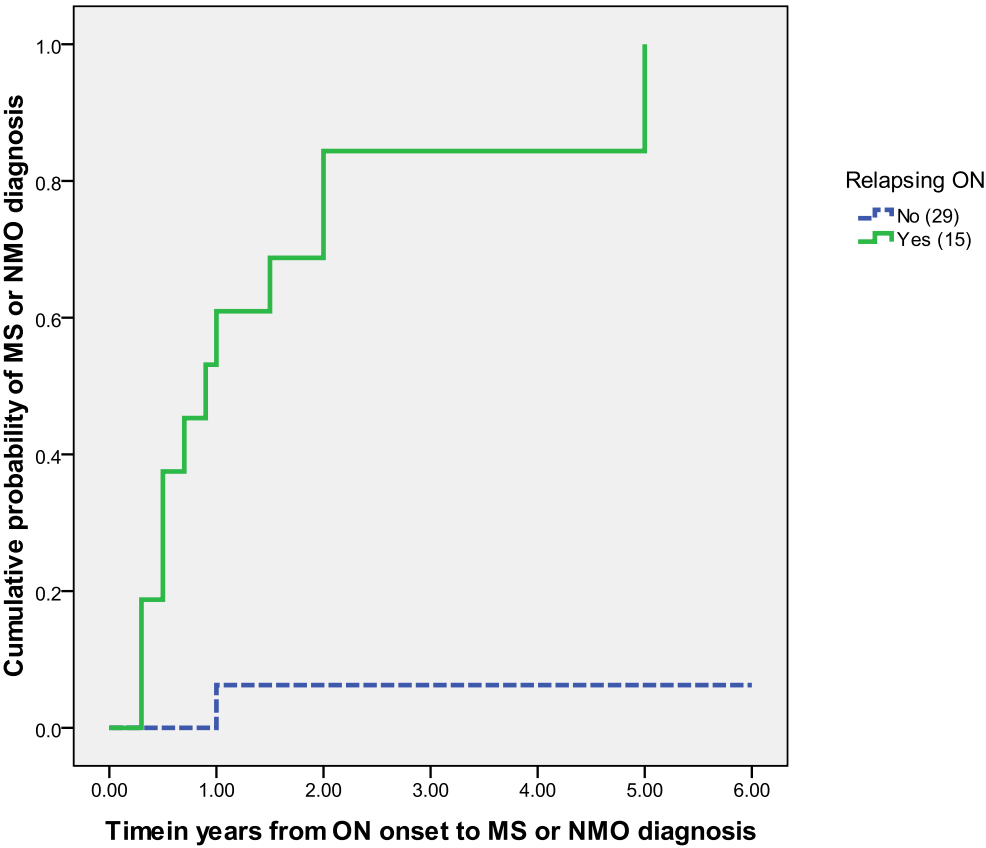
Investigation Findings

At presentation out of the 44 isolated ON cases, 38 (86%) had MRI brain imaging, of which 34% had white matter lesions other than in the optic nerve. A positive MRI for MS (s*ee* Figure 13) was a strong predictor for development of MS (logrank p<0.001). One patient with an initial normal MRI developed MS.

A total of 17 patients had CSF oligoclonal (OGB) band testing (Table 29). CSF OGB had poor sensitivity (50%) but good specificity (89%) and did not reliably predict progression to MS (Fisher exact test p=0.1, negative LR=0.56). Two patients who later developed NMO had negative CSF OGB. All three patients later diagnosed with NMO had NMO antibody testing after they had relapsed with transverse myelitis (after 0.3, 0.4, and 2 years) and diagnostic criteria were met .

Figure 13: Kaplan-Meier Curves showing cumulative probability of MS diagnosis after ON onset with positive or negative initial MRI
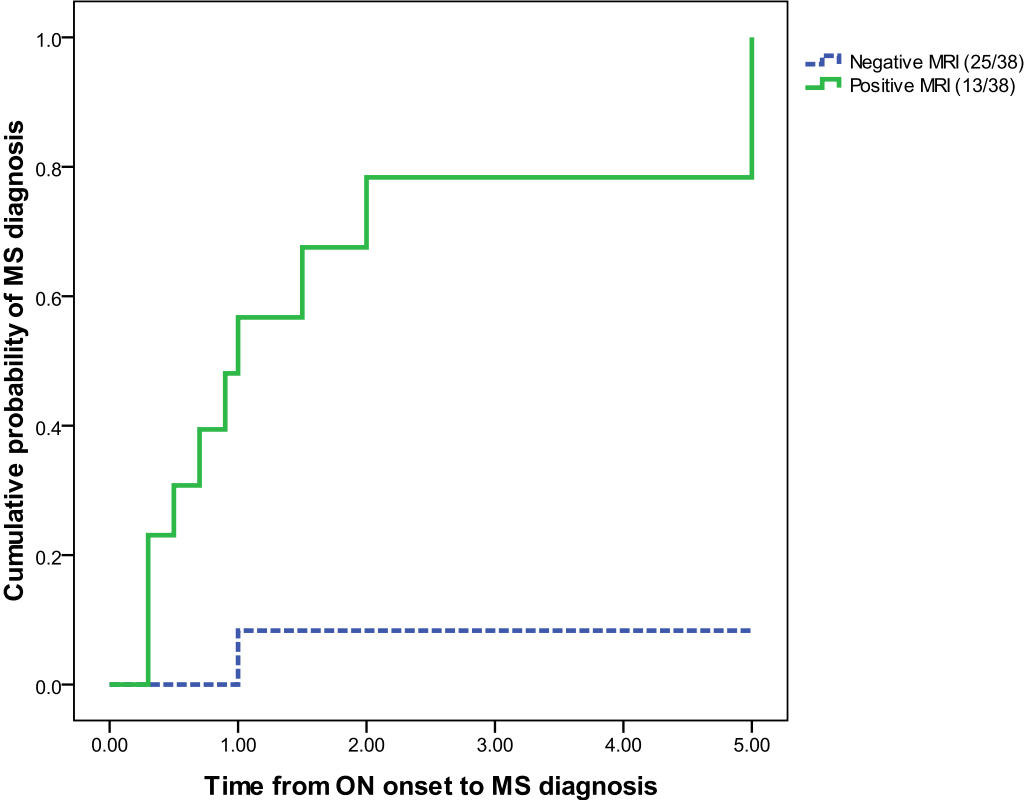
Table 29: CSF oligoclonal band testing results and outcome

	MS diagnosis on follow up	Monophasic ON/NMO
Positive CSF OGB	4	1
Negative CSF OGB	4	8

Treatment

Out of the 44 cases, 32 (73%) were documented to have received treatment with steroids. Administration and dosage varied widely, and the favoured regime was three days of intravenous methylprdenisolone (30mg/kg, maximum 1 gram) with various lengths (0 to 6 weeks) and doses of a prednisolone weaning regime. Children who had clinical CNS demyelinating relapses, and later diagnosed with Multiple Sclerosis by a Paediatric Neurologist were treated with disease modifying treatment (Rebif, BetaInterferon, or Copaxone).

DISCUSSION

Case series reported in the literature have tended to be single centre or smaller studies, not included NMO as an outcome, and some have included cases of polysymptomatic clinically isolated syndromes (CIS) at presentation(54-59). Our multi-centre study design utilised two sources for maximal case ascertainment, although capture-recapture analysis was not suitable due to problems with dependence and heterogeneity. Clear case definitions for inclusion and strict exclusion criteria were used at the outset. The retrospective nature as well as ascertainment being from tertiary centres raises the possibility of bias of case severity. The variable length of time to events, and follow of the study up was adjusted for by applying life table statistical analysis methods.

Acute optic neuritis in children differs from the typical adult form(56, 58, 213). Bilateral disease is thought to be more common in children, as is severe loss of visual acuity (6/60 or worse in 84% of eyes in one series, with recovery of visual acuity to 6/12 or better in 76% of patients)(56). In another recent case series involving 36 children, ON was unilateral in 58% and bilateral in 42%. Maximal visual deficit was severe in 69%, but full recovery occurred in

39 of 47 affected eyes (83%) (59). In our series ON was associated with severe visual deficit (<6/60 in 77%) with generally good visual recovery (70% in 41/59 eyes). Bilateral ON (57%) wasn't significantly more frequent than unilateral cases.

Age at presentation in our cohort (median 10.9 years) and a female predominance (ratio 1:1.8) was comparable to other studies(54-59). Neither variables (age greater than 10 years, and female predominance) reached significance levels.

As in adults, the condition is predictive of the subsequent risk of multiple sclerosis, although estimates of risk vary among studies. ON may also represent the first attack of Devic Neuro Myelitis Optica (NMO), an inflammatory, demyelinating condition in which clinical disease is referable to the optic nerves and spinal cord, without involvement of the remaining CNS white matter(214, 215). Devic NMO is associated with a high mortality (30%) in adults(214), but it is possible that the same process may have milder manifestations in children(216). Recently, a serum antibody that targets the aquaporin 4 molecule has been identified in Devic's NMO (60). In one longitudinal study, multiple sclerosis was diagnosed in 13% of children within 10 years after the first episode of optic neuritis, and in 19% within 20 years(58). In a Canadian cohort, 36% were diagnosed with MS at 2 years. In our study, I used lifetable analysis due to varying follow up lengths, and differing time points to relapse and MS or NMO diagnosis. The risk of MS or NMO development after isolated ON was high, with a cumulative probability of 0.45 at 2 years.

In our series a positive MRI at ON onset was a strong predictor for development of MS. Only one patient with a normal MRI developed MS. This data is comparable with that of the other cohort studies. In terms of other predictors, relapsing ON was also a strong predictor for MS or NMO development. Two case series have implicated bilateral (58, 59)as opposed to unilateral ON (57)as a predictor for development of MS, whilst one smaller series indicated

that female sex and an older age(57) indicated a higher MS risk after ON onset. Our study showed that gender, age (younger or older than ten years of age), unilateral/bilateral ON, and visual acuity severity did not appear to predict MS or NMO development.

Effects of corticosteroid treatment and other therapies on the recovery of visual function and on the risk of multiple sclerosis in children have not been established by randomized trials, but on the basis of data in adults, treatment with intravenous methylprednisolone is generally recommended if visual loss is unilateral and severe or is bilateral(213). Interferon therapy is considered in children with abnormal MRI scans of the brain, but data regarding the efficacy of therapy to prevent multiple sclerosis are lacking in this population. In our cohort 77% of cases received corticosteroid treatment with the favoured regime being three days of intravenous methylprednisolone with various lengths of a prednisolone weaning doses.

Our data suggests that childhood ON is associated with severe visual deficit with good recovery. The risk of development of MS or NMO was high. An initial abnormal MRI brain scan or relapsing ON should alert the clinician to MS or NMO diagnosis. A UK and Ireland population based prospective epidemiological surveillance study with multi-source case ascertainment is now underway to evaluate incidence rates and short term outcomes (at two years). Evaluating potential risk factors for early CNS demyelinating relapse and MS or NMO diagnosis may guide treatment guidelines and inform future longitudinal therapeutic trials.

3.2 Severe acute disseminated encephalomyelitis: a paediatric intensive care population-based study

Introduction

Acute disseminated encephalomyelitis (ADEM) is defined as an episode of inflammatory central nervous system (CNS) demyelination with polyfocal neurological deficits accompanied by encephalopathy (behavioural change or altered consciousness)(12). ADEM is more common in children than adults, although there are no adult epidemiological studies. Available population based incidence data of ADEM in childhood have reported an incidence of 0.7–4 per million children/year(31, 32, 38). There is often a wide variation in the severity of the illness. Occasionally, ADEM can present as a subtle disease, with nonspecific irritability, headache and somnolence. However, ADEM can present with a rapid progression of symptoms and signs to coma and decerebrate rigidity requiring admission to the Paediatric Intensive Care Unit (PICU), and may result in death(18). There is a paucity of literature describing the more severe life-threatening spectrum and its management. I describe a population-based study to determine the epidemiology, clinical characteristics, management and outcome of children with severe ADEM.

Methods

Severe ADEM was defined as requiring PICU admission or resulting in death. All 25 PICUs in England and Wales contributed towards data collected by PICANet between 2004 and 2008. PICANet is a UK national dataset which continuously records details of admission, discharge, diagnoses (coded using Clinical Terms 3 (The Read codes)), medical history, physiology, interventions and outcome. The Read codes (X001c ADEM – Acute disseminated encephalomyelitis; X001P Acute haemorrhagic leucoencephalitis; and X005 Subacute haemorrhagic leucoencephalitis) were used to search the database. The Paediatric Index of

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Mortality (PIM) scoring system was used to evaluate severity of illness(217). The PIM score is a simple model that consists of eight variables (type of admission; condition; response of pupils to light; base excess in blood; partial pressure of oxygen in arterial blood; fraction of inspired oxygen; systolic blood pressure; mechanical ventilation during first hour) measured at the time of admission to a PICU to predict expected probability of patient mortality (0–100%). The original version of PIM with recalibrated coefficients (218) was used. The Office for National Statistics (ONS) mortality database(219) (deaths registered in England and Wales (Series DR) 2009) which only provides ICD codes for cause of death and age ranges, was also searched as an additional method of case ascertainment of severe ADEM causing death. Equivalent ICD-10 codes (G4.0 – Acute Disseminated encephalitis; and G36.1 – Acute and subacute haemorrhagic leucoencephalitis) were used. Incident and mortality rates were calculated using a denominator from the mid-2006 England and Wales population estimates (10.2 million children younger than 16 years of age). Descriptive statistics were used to report on demographic and clinical features. Non-parametric tests (Kruskall–Wallis) were used to test the effect of age, PIM score, use of inotropes, and clinical features on length of ventilation days. Anonymised data were analysed using SPSS Statistics v17.0. Ethical approval for the collection of PICANet data, has previously been sought and obtained from a multi-centre research ethics committee (Trent Medical Research Ethics Committee ref. 05/MRE04/17) and collection of person-identifiable data has previously been approved by the Patient Information Advisory Group.

Results

In total, 27 PICANet ADEM cases (13 females, 14 males) were ascertained, giving a PICU population incidence for ADEM of 0.53 per million children/year (95% CI 0.36–0.76). There were three deaths (three female, aged 1–9 years) all ascertained via the ONS database, giving a mortality rate of 0.06 per million children/year (95%CI 0.02–0.2). The 27 PICANet cases which were available for further analysis had a median age of 4.8 years (range 1.0–13.8 years). Clinical features reported included: seizures (n ¼ 5), upper airway respiratory obstruction/stridor (n ¼ 2), polyfocal neurological deficits (n ¼ 6) and unspecified encephalopathy/encephalitis/encephalomyelitis (n ¼ 27). The number of children requiring invasive ventilation was 21/27 (78%), with median number of ventilation days =3 (interquartile range 1–5). Inotropes were used in four (15%) cases. One patient had invasive intracranial pressure monitoring. No patients received plasmapheresis. There were no children with acute or subacute haemorrhagic leucoencephalitis. The median PIM score was 4.00% (interquartile range 2.4–6.2%). PIM scores were <1% in 11% and 1–5% in 48%. All children were alive on discharge from PICU. Using the Kruskal–Wallis non-parametric test, only use of inotropes had a significant ($p < 0.05$) effect on length of invasive ventilation (Table 30). There was no observed effect on admission to PICU with regards to seasonality as measured by month of admission (October–March: 52%).

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Table 30: Kruskal-Wallis tests to explore effect of proposed predictor variables on length of ventilation days

Predictor	Number	Significance
Use of Inotropes (median length of ventilation days)	Yes= 4 (7.5 days) No= 23 (2.0 days)	0.027*
Seizures Respiratory obstruction Encephalopathy/polyfocal neurological	5 2 20	0.97
PIM score>5%; variables measured: 1. Type of admission to PICU 2. Specified condition 3. Response of pupils to light 4. Base excess in arterial or capillary blood, mmol/l 5. PaO2, mmHg 6. FIO2 at time of PaO2 7. Systolic blood pressure, mmHg 8. Mechanical ventilation at any time during first hour in ICU	11	0.92
Age > 7 years of age	7	0.29

Discussion

The incidence of childhood severe ADEM admitted to the PICU or resulting in death in England and Wales is approximately 0.5 per million children/year (32). This represents approximately a quarter of all children admitted with ADEM, with the denominator being 2009 Canadian ADEM incidence data of 2 per million children/year. The mortality rate described in this study indicates that ADEM results in death in approximately 3% of children affected. ADEM occurs more commonly in young children less than 10 years of age(18), and this is supported by our study. The sex ratios have previously been reported to be approximately equal (31, 38), and this is supported by our data. A seasonal distribution in the winter and spring months that has been found in studies conducted in the United States (38) was not observed in our severely affected cohort. The PIM scores for ADEM patients in this study were similar to those of national data of all patient admissions in 2005(220), (PICANet national report 2005), where 15.3% of PICU admissions had a PIM of <1% and 51.8% had a PIM of 1–5%. Respiratory failure secondary to brainstem involvement or severely impaired consciousness has previously been reported(18). In this study a large proportion of children required invasive ventilation for several days. Other indicators of severity are represented by the observation that inotropes were used in four (15%) cases, and one patient required invasive intracranial pressure monitoring. The clinical presenting features to PICU did not predict severity as measured by length of ventilation. However, cases that required the use of inotropes had a longer period of invasive ventilation. There are no controlled trials for the treatment of ADEM in childhood or adulthood. Most recommendations are based on observational studies. There is a consensus that intravenous corticosteroids should be administered in order to shorten the acute inflammatory process and hasten recovery(18). In cases of

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severe or life-threatening acute demyelination, plasmapheresis is usually considered in adults(160). Interestingly, none of the patients in our study received plasmapheresis. The database does not afford us enough information for us to comment if children responded to corticosteroids, or whether they received intravenous immuno-globulin. I speculate that the median number of ventilated days (n ¼ 3) would suggest a window where plasmapheresis could be considered prior to improvement. Thus it may be likely that a lack of clinical trials in children, practical procedural difficulties, and a lack of consensus amongst treating clinicians in the UK are reasons for the lack of use of plasmapheresis. Limitations of the study, that include the possibility of under-ascertainment, or misclassification as the case notes and magnetic resonance imaging (MRI) data were not available for review, preclude us from establishing long-term morbidity, outcome and best treatment. There are likely to be regional differences in the incidence of ADEM, and this has to be taken into account when interpreting estimates. In the PICANet dataset only six children were recorded as having polyfocal neurological deficits and unspecified encephalopathy, a widely accepted diagnostic criterion for ADEM. The diagnosis of ADEM is likely to have been made by a paediatric neurologist in conjunction with the evolution of clinical picture (not captured in dataset), and neuroimaging. However, it is important to acknowledge that the diagnosis of these children may indeed be of some variant of acute severe demyelination rather than ADEM. Our group has embarked on a surveillance study where all paediatric cases of CNS inflammatory demyelination in the UK and Ireland are being prospectively ascertained by active surveillance (paediatricians, paediatric neurologists, ophthalmologists) over 13 months (September 2009–September 2010), with detailed clinical and MRI data collected at the outset. This cohort will also be followed up for more detailed outcome data, and will enable validation of the new international

definitions. Nevertheless, this intensive care cohort provides important insights into the

epidemiology and management of severe ADEM.

3.3 Paediatric multiple sclerosis: examining utility of the McDonald 2010 criteria

Introduction

Paediatric multiple sclerosis (MS) is becoming increasingly recognized, (221) with up to 10% of adults having their first symptoms in childhood. (222, 223)Magnetic resonance imaging (MRI) is increasingly utilized in aiding the prompt diagnosis of MS in children. (224) Currently the International Paediatric MS Study Group (IPMSSG) recommends that paediatric MS diagnosis is based on McDonald 2001 MRI criteria (225, 226) whilst eliminating any lower age limit. In addition, the IPMSSG state that an episode of acute disseminated encephalomyelitis (ADEM) cannot be considered as the first event of MS, unless a second non-ADEM demyelinating event is accompanied by further evidence of dissemination in time (DIT) (either with new MRI T2 lesions ≥3 months from the second event, or a new [third] clinical event developing ≥ 3 months subsequent to the second event). Recently the new McDonald 2010 diagnostic criteria, for the first time, have been recommended for use in children with acute demyelination presenting with a clinically isolated syndrome (CIS)(227). Common and important to both the McDonald 2001 and McDonald 2010 MRI criteria is the requirement of lesion dissemination in space (DIS) and time (DIT). The McDonald 2001 criteria state DIS can be fulfilled if three out of four features are satisfied: (1) nine or more T2 white matter lesions or one gadolinium-enhanced lesion; (2) one juxtacortical lesion; (3) three periventricular lesions; (4) one infratentorial lesion. The McDonald 2001 DIT criteria are fulfilled if new T2 lesions or gadolinium-enhanced lesions develop after 3 months following the initial attack (225). McDonald 2010 criteria state that DIS criteria are fulfilled if one or more T2 lesion is present in two out of four areas: (1) juxtacortical; (2) periventricular; (3) infratentorial; (4) spinal

cord (if the patient has a brainstem or spinal cord syndrome, symptomatic lesions are excluded from the criteria and do not contribute to the count). McDonald 2010 DIT criteria can be fulfilled if a new T2 and or gadolinium-enhanced lesion is present on follow-up MRI irrespective of the timing of a baseline MRI, or if there is simultaneous presence of gadolinium-enhanced and non-enhanced lesions at any time (including at time of first scan). Previous retrospective MRI paediatric MS studies have shown McDonald 2001 criteria lack sensitivity for diagnosis of paediatric MS (224, 228). The same study groups have also shown that McDonald 2001 MRI criteria have high specificity and differentiated children with MS from those with relapsing non-demyelinating disorders with central nervous system (CNS) involvement, such as migraine and small vessel vasculitis (228).I hence aimed to assess the utility of the new McDonald 2010 criteria in comparison with the 2007 IPMSSG criteria for the early diagnosis of paediatric MS, and also compare these criteria in a cohort of children with relapsing non-demyelinating neurological disorders. To our knowledge this is the first study examining the McDonald 2010 criteria in a paediatric cohort.

Methods

Cases with clinically definite relapsing–remitting MS (229) from three tertiary UK paediatric demyelination clinics were retrospectively identified using hospital databases for MS. The demyelination clinics are led by paediatric neurologists with a specialist interest in MS and allow comprehensive and longitudinal evaluation of children with CNS inflammatory demyelination. Consecutive cases of children younger than 16 years old with a first demyelinating episode (post publication of McDonald 2001 criteria; 2001–2009) and with both initial (within 3 months of clinical onset) and first follow-up scan (routine or relapse

associated) available for review were included. All MRI scans were performed on 1.5T scanners. DICOM viewing software (IMPAX version; © 2007 Agfa HealthCare, Mortsel, Belgium) was used to view scans. Sequences used included, T1, T2, T2 FLAIR ± gadolinium-enhanced. A standardized MRI protocol was not used as this was a retrospective study based on collecting data from established clinical practice. MRI slice thickness varied from 3–5 mm. MRI scans were examined for the presence of DIS and DIT criteria which allowed diagnosis via the McDonald 2001 criteria and McDonald 2010 criteria, respectively. Two assessors reviewed scans and reports, with consensus agreement with regards lesion number and location, and then inputted anonymised data into a standardized Excel spreadsheet. Migraine patients (International Headache Society Criteria (230) with MRI brain T2 white matter signal changes with or without other CNS manifestations were used as controls (age and sex matched to patients with MS). Statistical analysis was performed using PASW Statistics for Windows version 18.0 (© SPSS, Inc., 2009, Chicago, IL, www.spss.com). Descriptive and non-parametric statistics were used (binomial, Fishers exact, Kruskal–Wallis, and McNemar tests) to summarize key aspects of the dataset. Ethical approval was deemed not necessary for this retrospective evaluation of criteria for routine clinical practice (National Research Ethics Service and National Patient Safety Queries Line 17/06/2011) and confidentiality of patients was maintained (data anonymised and cases cannot be identified).

Results

The initial search identified 49 patients, 11 of whom were excluded due to: lack of availability of initial or first follow-up scan for review (two patients); MS diagnosis not

clinically confirmed (two patients); monophasic ADEM (three patients); multiphasic ADEM (two patients); or neuromyelitis optica (two patients). In total, 38 children with MS (Table 1) were included, 28 female and 10 male (p = 0.005). The median age of onset was 12.9 years (25–75th centile = 10.5–14.3 years) and duration of follow-up was median 3.5 years (25–75th centile = 2.3–4.6 years). Clinical features at first presentation of the MS cohort included: optic neuritis (16 patients); cerebellar (12 patients); pyramidal (11 patients); brainstem (10 patients); headache (seven patients); hemisensory (five patients) and myelitis (four patients). One patient presented with encephalopathy on initial attack but had two subsequent CIS relapses consistent with MS. Time to first relapse was median 0.6 years (25–75th centile = 0.3–0.8 years) and median relapse rate was 0.8 relapses/year (25–75th centile = 0.4–1.5 relapses/year). Cerebrospinal fluid oligoclonal bands were positive in 23/31 (74%) and aquaporin-4 antibody was negative in 6/6 patients tested. Twenty-nine children were given disease modifying treatment (DMT) in the form of interferon 1a (seven patients), interferon 1b (17 patients) or glatiramer acetate (five patients) at a median age of 13.7 years (25–75th centile = 12.4–15.9 years). All patients had T2 white matter brain lesions at first MRI (Table 2). The McDonald 2001 DIS criteria were fulfilled in 26/38 (68%) at first scan, whilst McDonald 2010 DIS criteria were fulfilled in 32/38 (84% p = 0.03). Only 18 patients had gadolinium contrast administered at first scan, of which 11 showed lesion enhancement (61%) hence fulfilling McDonald 2010 DIT criteria. The 11 children who had gadolinium contrast upon their initial scan also fulfilled McDonald 2010 DIS criteria, and hence fulfilled a diagnosis of MS at first presentation. On follow-up MRI, 3/38 (8%) children failed to meet the McDonald 2001 DIS and DIT criteria, whilst all children fulfilled McDonald 2010 DIS and DIT criteria. Eighteen control cases were matched for age and sex to MS cases. The median age was 10.9 years for both groups (MS cases 25–

75th centile = 8.1–14.1; control 25–75th centile = 7.7–14.2, p = not significant). Six control cases had follow-up imaging at a median of 0.7 years (range: 0.3–2.1 years). There was no significant difference between the number of total T2 white matter lesions found in MS and controls (Table 3). Of those control cases given contrast (n = 2) at first scan, none showed enhancement. Only 1/18 control case fulfilled both the McDonald 2001 and McDonald 2010 DIS criteria at first scan. This case did not fulfil the McDonald 2001 or McDonald DIT criteria on follow-up scan (was never given contrast). Of the five other control cases that had a follow-up scan performed, all failed to meet DIS and DIT according to both the McDonald 2001 criteria and McDonald 2010 criteria.

Discussion

To my knowledge this is the first study examining the utility of the new McDonald 2010 criteria in a paediatric MS cohort. The 2010 McDonald criteria allow MS diagnosis on the first scan and may allow diagnosis at first presentation of CIS in at least a half of paediatric cases. In addition, our study confirms that on follow-up imaging, the McDonald 2001 MS criteria (currently recommended by the IPMSSG) were met by fewer patients in contrast to McDonald 2010 criteria. This study also supports the hypothesis that children presenting with typical clinical features of a CIS consistent with CNS inflammatory demyelination (227) should be given gadolinium to allow for earlier diagnosis. The abolition of specific time limits, as those of the older criteria, (226) may make it easier for paediatric neurologists with an interest in MS to decide on early treatment of their patients and allow for prompt entry in to future paediatric clinical trials. From the control group, only one control case fulfilled the McDonald 2001 and McDonald 2010 DIS criteria but did not fulfil DIT criteria on

follow-up. This is potentially reassuring, given that the new simpler criteria did not perform differently when compared with the more stringent established criteria. Limitations of this study include: its retrospective nature; the fact that it contains cases with confirmed clinically definite MS as opposed to being a prospective follow up cohort study at first CIS presentation; that not all children had spinal imaging and contrast administered; the relatively small numbers precludes testing subgroups; and that MRI sequence variation could affect the sensitivity of results. Nevertheless the study provides useful data towards assessing the utility of the new McDonald 2010 criteria in children. Future longitudinal prospective studies are required to further evaluate these criteria in children presenting with a first episode CIS.

3.4 Prognostic factors for paediatric NMO and NMO spectrum disorders

INTRODUCTION

Neuromyelitis Optica (NMO) is a severe and rare inflammatory condition characterised by the presence of both optic neuritis and transverse myelitis occurring simultaneously or separated in time and distinct from multiple sclerosis. Auto-antibodies to the astrocytic water channel protein Aquaporin-4 (AQP4-Ab) AQP4 (60) are found in the majority of cases and are believed to be the cause of the observed astrocytic and myelin damage. The discovery of AQP4 antibodies has broadened the disease spectrum. AQP4-Ab appears to be a specific test as it is invariably negative in MS patients of all ages (61, 62). NMO usually presents as an isolated optic neuritis (63) (64) or as TM before further relapses reveal the underlying diagnosis (63). It is usually a relapsing remitting disorder unless treated with immunosuppression. NMO comprises 3-8% of the childhood Acquired demyelinating syndromes (61) and needs to be distinguished at onset from the commoner disorders namely multiple sclerosis, acute disseminated encephalomyelitis and idiopathic monophasic transverse myelitis. The revised diagnostic by Wingerchuck et al.(66), which are also accepted by the paediatric international MS study group (IPMSSG)(12); require two absolute criteria: (i) optic neuritis; (ii) myelitis; and at least two of three supportive criteria: (i) Spinal cord MRI lesion extending >2 vertebral segments; (ii) MRI criteria not satisfying the revised McDonald diagnostic criteria (67) for MS; (iii) AQP4-Ab in serum.

Table 31 summarises the clinical features in the three recent case series of paediatric NMO using diagnostic criteria *(61, 68, 69).* Importantly, out of the 38 NMO cases described in the three studies, only 16 (42%) tested negative for AQP4-Ab. In children as in adults (168), AQP4-Ab negativity is associated with recurrence and higher risk syndromes. In addition although brain involvement is increasingly recognised in NMO, yet the MRI features are still not well delineated. It is important to recognise NMO early as permanent disability is more attack-related in NMO than in MS. In paediatric practice, clinicians are often uncertain as to when to test for AQP4-Ab in children presenting with their first onset acquired demyelinating syndrome. I have previously reported in a national incident cohort (n-125), that of those for the AQP4-Ab (n=52), one child with optic neuritis and both Wingerchuck criteria positive NMO patients tested positive for AQP4-Ab; whilst none of the ADEM, TM, and other CIS cases tested positive(231). Very early onset NMO onset as occurs in children may inform different aspects of the disease such as MRI lesions, disability progress and other associated features.

Table 31: Summary of recently described paediatric NMO case series (61, 68, 69)

Ref	Setting, Design & Criteria Used	Demo-graphics	AQP4-Ab & CSF OGB	First attack & course/ Time to first relapse/ Annualised relapse rate (ARR)	MRI Brain features	Disease Modifying Treatment	Outcome/ disability
Collongues 2010	Multicentre (mainly adult); retrospective; France; Follow up mean 19.3 yrs; Wingerchuk 2006 criteria	12 cases Age: 14.5 yrs median (4.1-17.9) 3F:1M	8/12 AQP4-Ab positive	First attack: 6ON/5SC/1OS All relapsing-remitting; first attack interval 17 months (7–154)	6/12 MRI brain abnormal (1-10 lesions) 3 MS radiological criteria positive (2MS/1ADEM) 0 Barkhof	All treatments used: Azathioprine; cyclophosphamide; glatiramer acetate; IVIG; interferon; mitoxantrone; MMF; rituximab	Median time to EDSS 4= 20.7 yrs Vision: residual visual loss +1 logMAR or 20/200 Snellen=1.3 yrs.
Lotze 2008	Retrospective single centre; USA; Follow up 4 yrs median (0.6-9); Wingerchuk 2006 criteria	9 cases Age: 14yrs median (1.9-16); All female	6/9 AQP4-Ab positive (1 had recurrent TM only)	First attack: 5 OS/1TM/2ON All relapsing ARR=2.6	9/9 MRI brain abnormal (5 symptomatic)	All treatments used: 6 steroids + MMF 5 rituximab 1 monthly IVIG 1had azathioprine, glatiramer, and monthly PLEX.	Median EDSS=3 (range 0-8)
Banwell 2008	Selected prospective cohort; Canada & Argentina; Follow up 36 months median (1.2-126 months); Wingerchuk 1999	17 cases Age: 10.4 yrs median (4.4–15.2) 3.2F:1M	8/17 AQP4-Ab positive 13 CSG OGB negative (1 recurrent ON, and 1 recurrent TM AQP4-Ab positive; 68 other CNS inflammatory demyelination were negative)	9 relapsing (AQP4-Ab pos) 8 monophasic (AQP4-Ab pos)	9/17 MRI brain abnormal	At time of serum: 7 prednisone, 1 glatiramer acetate, 1 interferon-1a, 2 monthly IV cyclophosphamide	1 non-ambulant, 1 gait limited aid not required; Vision: 12/18 decreased visual acuity or severe visual impairment (4/18)

ADEM= Acute Disseminated Encephalomyelitis; ARR= annualised relapse rate; EDSS= Expanded Disability Status Scale; IVIG= intravenous immunoglobulin; MMF= mycophenolate mofetil; MRI= Magnetic Resonance Imaging; MS= Multiple Sclerosis; AQP4-Ab= Neuromyelitis Optica antibodies; ON= Optic Neuritis; OS= Optico-spinal; PLEX= plasmapharesis; SC= Spinal Cord; yrs= Years

I aimed to collect details of paediatric NMO and spectrum disorder cases to describe the clinical; MRI features; outcome; and prognostic features in relation to the AQP4-Ab status.

METHODS

I conducted retrospective case ascertainment and case note review of paediatric (<17 years) cases from four UK paediatric demyelination centres and / or patients known to the UK national NMO service (Table 2). MRI scans previously reported by a neuroradiologist were also reviewed at multidisciplinary NMO meetings Inclusion criteria used were the Wingerchuk 2006 criteria or AQP4-Ab positivity.

Descriptive statistics, univariate associations, and Kaplan-Meir lifetable analysis were used to explore differences between AQP4-Ab positive/negative cases and predictors for relapse.

In addition the MRI characteristics of the NMO cohort were compared to those of a national cohort selected sample of known AQP4-AB negative cases and not satisfying Wingerchuck criteria but with abnormal MRI brain scans(231).

RESULTS

Demographics

A total of 22 cases were ascertained (Table 32) of which 19 were females (86%) and 14 were AQP4-Ab positive (64%). The median age of onset was 9.4 years (range 2.9-16.8 years) and median follow-up time was 5.9 years (range 1.5-17 years).

Table 32: (A) NMO Cohort description (B) Phenotype of first relapse relative to the first attack

A. NMO Cohort description		AQP4 status		Significance	TOTAL NMO cohort n=22		Demyelination cohort (n=29)
		AQP4 neg (n-8)	AQP4 pos (n=14)				
Sex	**Male: Female**	0:8	3:11	p=0.17	3:19		13:16
Age at onset (years)	**Median Range**	10.9 (5.4-16.8)	9.3 (2.9-15.0)	p=0.50			13.6 (1.3-15.8)
Follow up duration (years)	**Median Range**	5.4 (1.5-12.0)	6.1 (1.8-17.8)	p=0.92			1.0
Wingerchuck 2006 criteria positive		8/8	12/14		20/22		0/29
First presentation/ cohort phenotype	**unilateral ON** **bilateral ON** **TM** **TM and ON** **ADEM**	2 2 2 2 0	7 2 2 1 2	p=0.38 (for unilat ON)	9 4 4 3 2		ADEM=3 ON=2 TM=11 MS= 13
MRI brain changes present		5/8	10/14	p=0.67	15/22 (65%)		29
CSF OGB- positive		0/7	2/11	p=0.25	2/18		10/19
Relapsing		6/8	13/14	P=0.25	19/22		n=11
Phenotype of first relapse	**unilateral ON** **bilateral ON** **TM** **TM & ON** **CIS/ADEM**	3 0 2 0 1	5 0 5 1 2	n/s	8 0 7 1 3		n/a

B. Phenotype of first relapse relative to the first attack		Phenotype of first relapse			
		unilateral ON	TM	TM and ON	CIS/ADEM
First presentation	unilateral ON	5	1	1	1
	bilateral ON	2	2	0	0
	TM	1	2	0	0
	TM and ON	0	1	0	1
	ADEM	0	1	0	1

At presentation: 9 had unilateral ON; 4 had bilateral ON; 4 had TM; 3 had simultaneous TM & ON; 2 acute disseminated encephalomyelitis. A half (11/22) of cases had a brain syndrome episode during the disease course and 20/22 (91%) had LETM. Table 2 also represents the phenotype of the relapse relative to the first attack. Differentials diagnoses recorded included: osmotic myelinolysis; mitochondrial; metabolic; ADEM; multiple sclerosis; isolated ON or TM; tumour.

MRI

Six of twenty-two cases (27%) had an abnormal brain MRI at disease onset, and 14/22 (64%) had an abnormal MRI brain on follow up (Figure 14). Eleven out of 14 (79%) had an abnormal within first year). Table 33 describes MRI brain lesion location and characteristics in the NMO cohort, as compared to the acquired demyelinating national sample.

Table 33: MRI lesion location and characteristics in NMO patients as compared to an incident national cohort with abnormal MRI scans

		n=14 NMO cases with abnormal MRI brain (out of 22)	N=29 Acquired demyelinated syndromes from a national cohort (non-NMO and AQP4-Ab negative)
Location	Centrum semiovale / Deep White Matter	7 (50%)	16 (55%)
	Periventricular	7 (50%)	14 (48%)
	Brainstem	6 (43%)	12 (41%)
	Thalamic/ basal ganglia	5 (36%)	5 (17%)
	Juxtacortical	5 (36%)	14 (48%)
	Periaqueductal grey	5 (36%)	n/a
	Cerebellar	4 (29%)	7 (24%)
	Corpus Callosum	4 (29%)	10 (34%)
	Hypothalamic	3 (21%)	n/a
	Cortical	2 (14%)	4 (14%)
Nature of lesion	Large	10 (71%) *	9 (31%)
	Acute lesions mostly resolving on repeat	8 (57%) *	4/22 (18%)
	T1 hypointense	6 (43%) *	3 (10%)
	Gadolinium enhancing	5 (33%)	6/17 (35%)
	Barkhof	3 (21%)	11 (38%)
	LETM	20/22 (91%) *	11/29 (38%)

*Fisher's exact test p<0.05

Figure 14: NMO MRI Brain Scans
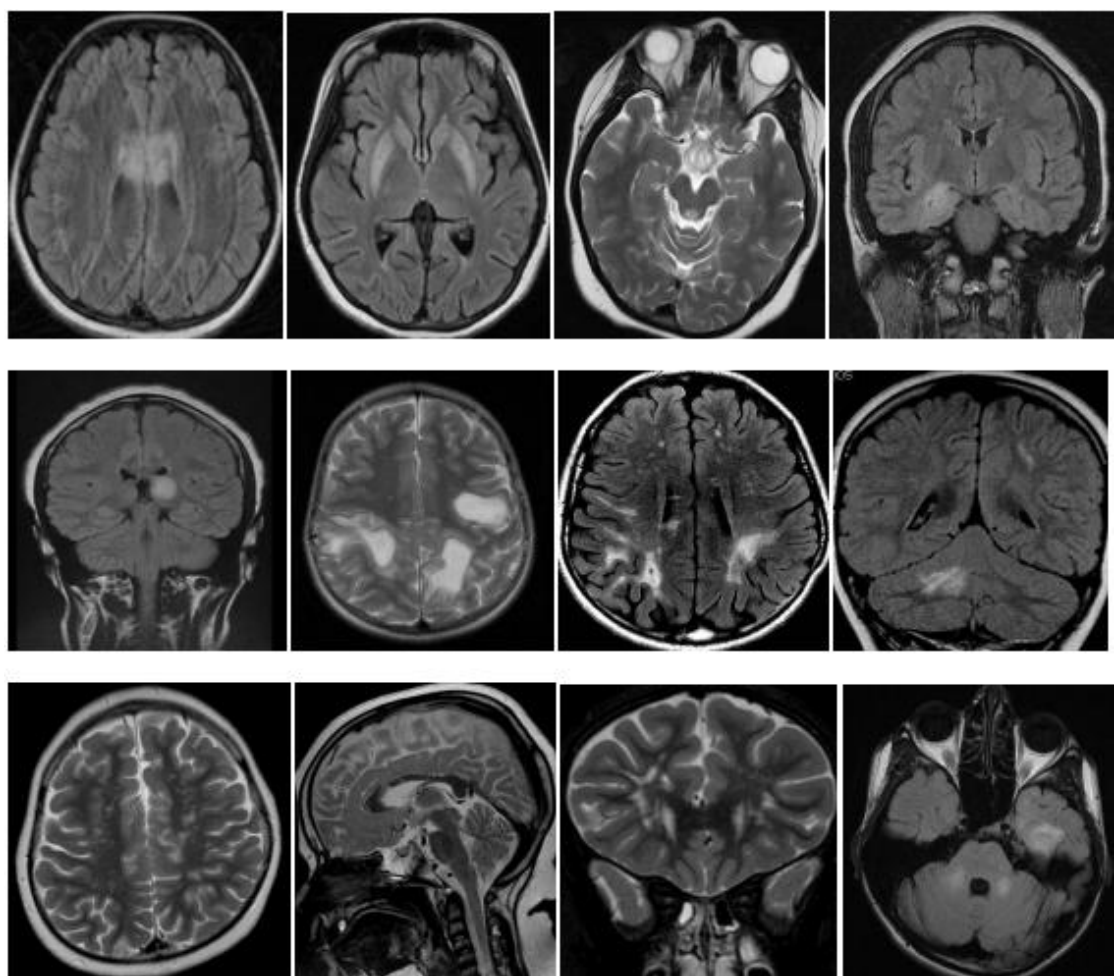
Relapse

Using life table analysis (Figure 15), mean time to relapse was 2.4 years in AQP4-Ab negative cases (95% CI 1.1-3.6 years) vs 0.76 years (95% CI 0.43- 1.1 years) for AQP4-Ab positive cases (p=0.03 log rank test -mantel-cox). Six out of eight AQP4-Ab negative cases were relapsing vs 13/14 AQP4-Ab positives. The annualised relapse rate for AQP4-Ab positive cases was 0.70/ year vs 0.38/ year for AQP4-Ab negative cases (z score=2.316; p=0.21).

Figure 15: Kaplan-Meier curves showing cumulative probability of relapse after first attack for children with AQP4-Ab positive NMO vs AQP4-Ab negative NMO
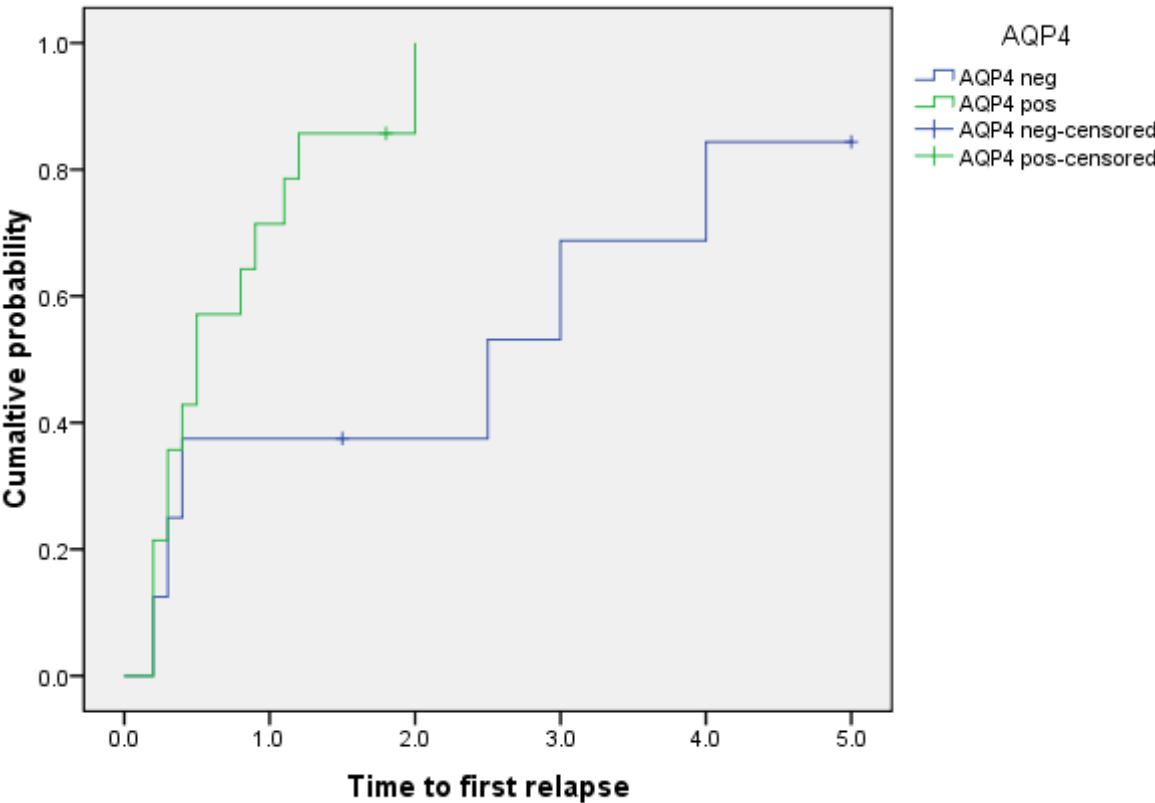
In order to conduct a clinical trial to reduce ARR from 0.70 to 0.35: a sample size requires based on a negative binomial model with a dispersion index k of 0.43; power =80%; alpha=0.05; would require a sample size of n=84 per arm.

Outcome

AQP4-Ab positive cases 11/14 had visual acuity of <6/60 snellen in at least one eye (0/8 in AQP4-Ab negatives). Three cases were wheelchair dependent on follow up (AQP4-Ab negative).

DISCUSSION

I describe a historical NMO longitudinal cohort with known AQP4-ab status and compare it to a contemporary incident national cohort sample. As in other adult and paediatric series, NMO predominantly affects females. Interestingly all 8 AQP4-Ab NMO cases were females.

At presentation a large proportion of children had optic neuritis (73%) compared to transverse myelitis (32%). Importantly two of the 22 cases presented with an acute disseminated encephalomyelitis, hence potentially delaying AQP4-Ab testing. A half of cases had a brain syndrome episode during the disease course and the majority (91%) had LETM. As in other case series NMO is a relapsing disease with AQP4-AB positivity associated with higher relapse rates compared to AQP4-Ab negativity.

The National MS Society task force on differential diagnosis of MS, (27) described MRI brain abnormalities which were more likely indicative of NMO in adults as opposed to MS: 1. Non-

specific brain T2-signal abnormalities not satisfying the Barkhof criteria for dissemination in space used in the revised McDonald criteria; 2. lesions in the dorsal medulla; 3. hypothalamic and/or brainstem lesions; 4. linear periventricular/corpus callosum signal abnormality, but not ovoid, not extending into the parenchyma of the cerebral hemispheres in Dawson finger configuration. Brain lesions in paediatric NMO appear to occur more commonly (>50%) when compared with adult NMO (25%) (63). In one series (61) 9/17 (53%) children with NMO (Wingerchuk et al., 2006) had brain lesions. Our cohort confirms that brain involvement is common in paediatric NMO with nearly two thirds having an abnormal MRI brain scan. In a recent case series (69) showed that the first brain MRI in paediatric NMO (as defined in Wingerchuk et al., 2006) can show a diffuse inflammatory process, such as MS-like (2 patients) or acute disseminated encephalomyelitis-like lesions (1 patient). Brain lesions in another series (68) also confirm this observation and demonstrated that MRI brain changes in paediatric NMO frequently involve the diencephalon. In our cohort over one quarter of children had an abnormal MRI brain scan. In childhood NMO, lesions located in the hypothalamus, brainstem, or cerebral white matter, have been described. In our cohort Lesion location did not appear to differentiate both samples but NMO lesion nature appeared different. NMO brain scan lesions compared to the acquired demyelinating cohort: tended to be large (>2 cm); acute lesions largely resolved on repeat scan; and often had T1 hypointense lesions. It is important to recognise the spectrum of brain abnormalities in NMO as the occurrence of such lesions and sometimes the presence of encephalopathy and polyfocal neurological deficits may resemble ADEM, with misleading implications as to prognosis and therapy.

It is important to recognise NMO early in the course of the disease as permanent disability is more attack-related in NMO than in MS (168). Hence, early and aggressive intensive treatment with disease modifying treatment may be beneficial in reducing the disability and ameliorating the course of disease in children (27, 61, 68, 69, 168). There have been no large randomised trials in children or adults and current practice is based on case series and expert opinion. Recent adult European consensus guidelines have been published (168). A wide variety of disease modifying drugs have recently been used but recent reports show that drugs used to treat multiple sclerosis (interferons, glatiramer) may exacerbate NMO (169). Although rare, early AQP4 testing may allow diagnosis and prompt immunosuppressive treatment. Clinical trials with designs for rare diseases are needed early in the disease course but with long term follow up in order to determine best treatment strategies in children with NMO.

Paediatric NMO has been reported to have a better prognosis than adult NMO in terms of disability. In one study median time from onset to Expanded Disability Status Scale (EDSS) 4 ([significant disability but self-sufficient and able to walk without aid for approximately 500m] 20.7 vs 5.3 years; p <0.01) and EDSS 6 ([requires a walking aid to walk about 100m]26 vs 8.5 years; p <0.01) was largely explained by the increased severity of the first myelitis in the adult NMO group (69). In contrast, a USA paediatric NMO-spectrum series showed residual disability in 43/48 patients (90%) with 54% having visual impairment (27% blind) and 44% motor deficits (median Expanded Disability Status Scale 4.0) at 12 months (71). In this cohort, childhood NMO is associated with clinical relapses and disability. AQP4-Ab positivity is associated with early recurrence and visual disability.

NMO may be difficult to identify at first presentation due to similarity of clinical and MRI phenotype with other acquired demyelinating syndromes. MRI brain lesion characteristics

and early MRI repeat scans may be useful to raise suspicion. In order to be alert to early visual failure in this rare disease, widespread AQP4-Ab testing may be needed as a standard investigation at first demyelination presentation.

3.5 Early outcomes and predictors after a first episode of an acquired demyelinating syndrome

Aims

In this section, I report on the outcomes from the British Isles (UK, Ireland, & Channel Islands) multisource prospective active surveillance study (See chapter 2.1 for a description of case ascertainment, methods, and incidence). The primary objective of the follow up of cases in this chapter is to determine the following outcomes following a first episode of CNS Inflammatory Demyelination: occurrence of a relapse; multiple sclerosis diagnosis as per the International Paediatric MS Study Group (IPMSSG) criteria;   evidence of disability as per the EDSS functional scores.

Secondary objectives were:

- to report distribution of MS diagnosis by age, sex and ethnic group

- to report MRI features of childhood MS

- to classify diagnostic categories by using the IPMSSG consensus definitions for MS diagnosis (including the incorporated McDonald MRI 2001 and Barkhof space diagnostic as recommended by IPMSSG criteria).[1, 2]

- to investigate the sensitivity and specificity of MRI criteria and prognostic models proposed for children, including the newly revised 2010 McDonald space and time diagnostic criteria;(22) and the recent Verhey MRI prognostic model MS criteria using the IPMSSG MS criteria as the reference standard (193).

- Consideration of risk factors with exploratory analyses for phenotypic characteristics in predicting MS

- to describe the frequency with which proposed clinical, investigative and MRI features for MS occur in children.

Methods

Study Design

I carried out a one year follow up study, by following up positive cases reported from the prospective active surveillance study of first episode ADS in children aged between 1 and 15 years.

Case follow up

After the one year follow up date, I contacted the original reporting clinicians throughout the UK & Ireland directly, by sending a data collection form to capture outcome data. Minimal identifiers (National Health Service [NHS] number, district postcode, sex and date of birth) were used to help the clinicians identify cases they have reported. A reminder email and letter was sent at 2 months if nothing was returned. MRI copies and/or reports were collected where possible.

Definitions

A relapse is a new occurrence of neurological symptoms that lasted > 24 hours and stabilized or resolved either partially or completely. Table 34 describes the paediatric ADS forms of relapsing disease.

Table 34: IPMMSG Definitions of relapsing disease

Condition	Definition
Recurrent and Multiphasic Acute Disseminated Encephalo-myelitis (R-ADEM & ADEM)	If a new event occurs ≥3 months after the first ADEM attack and ≥1 month after completing steroid treatment, it is defined as: . Recurrent ADEM: recurrence of initial symptoms without involvement of new clinical areas. . Multiphasic ADEM: New event, but involving new anatomical areas of the CNS.
Multiple Sclerosis	- Two or more episodes of CNS demyelination separated in time and space: - Dissemination in **space** requirement can be met if: MRI shows three of: 1) nine or more white matter lesions or one gadolinium enhancing lesion, 2) three or more periventricular lesions, 3) one juxtacortical lesion, 4) an infratentorial lesion. OR combination of an abnormal CSF (oligoclonal bands or elevated IgG index) and two lesions on the MRI (one in the brain). - Dissemination in **time** requirement can be met if: MRI shows new T2 or gadolinium enhancing lesions developing 3 months following the initial event.
Neuro-myelitis Optica (NMO)	Must have: i. Optic neuritis and ii. Acute myelitis. Must have: Spinal MRI lesion extends over three or more segments or iv. Aquaporin-4 antibody testing is positive. The brain MRI may be abnormal but must not meet Multiple Sclerosis MRI diagnosis criteria.

Data Collection:

A targeted neurological and outcome history (using a check box questionnaire) was requested, and data collected was broadly categorised to document: (See Appendix Surveillance Outcome Questionnaire)

- Occurrence of a relapse

- Demyelinating symptoms and signs

- Information which might confirm the development of recurrent ADEM, multiphasic ADEM, or MS, for example the anatomic distribution (optic nerve or spinal cord, monofocal or multifocal distribution), CSF findings, serological and neuroimaging results.

- Treatment of relapse (eg, steroids, immunoglobulins, intensive care) given and duration of hospital stay.

- Disability outcomes including: motor- using the EDSS scale; attainment at School; vision loss; fatigue; new onset of seizures.

MRI imaging review

All cases already had had their initial MRI scan reviewed as described in Chapter 2.1. Data from any follow up MRI scan results was collected, and when available, scans were reviewed blinded to clinical features jointly by MA and one of five neuroradiologists. A standardised proforma was completed utilising previously described nomenclature (see x) [5-7]. McDonald 2001 dissemination in space criteria (as recommended by the current IPMSSG criteria),[1, 2] McDonald 2010 dissemination in space and time criteria (if a gadolinium enhancing scan was available) and Verhey prognostic model were applied by MA according to the MRI variables.(22) All MRI brain scans were performed on 1·5T scanners and had a

minimum of a T1 weighted, and a T2 weighted or fluid-attenuated inversion recovery (FLAIR) sequence in two different planes. Additional sequences included gadolinium-enhanced T1, diffusion weighted and spine images. MRI slice thickness varied from 3–5 mm.

Disability outcomes

At one year, clinicians were asked to complete outcome questionnaires (see Appendix). Questions were designed to closely map onto the Kurtzke functional systems (pyramidal, cerebellar, brainstem, sensory, sphincter, mental, and visual functions) and the expanded disability status scales (EDSS) (232). The Kurtzke and EDSS scales have long been the accepted scales for disability in adulthood multiple sclerosis, although there are many limitations (233), which include: its emphasis on motor function; insensitivity to change; insensitive to patient reported outcomes and of quality of life; and only moderate inter- and intra-rater reliability (234, 235). They can also be somewhat complex to score to the unfamiliar busy clinician. By using questions familiar to paediatricians, and by using one scorer, I aimed to ensure with scoring measures. In addition, other questions were also asked of the reporting clinician, such as presence of fatigue and symptoms of depression to try and obtain as complete a picture as possible, whilst acknowledging clinician time constraints. The following question were hence asked (also see appendix xx for questionnaires) of clinicians, and data additionally also mapped on to the EDSS (see Table 35 below):

1. Mobility/ motor skills

- whether the patient had a motor impairment or limitations on mobility?

- whether participation was limited due to gait

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- the frequency of walking aids and wheelchair use

- whether weakness was present due weakness in arm (s) and/or legs(s)

- ataxia of the limbs present

- difficulties with fine motor skills

- loss of sensation

- rehabilitative therapy required

2. Vision:

- whether the case had poor visual recovery (ie. worse than a snellen of 6/9 or to previous

  level of visual acuity if pre-existing impairment)

- level of visual acuity in each eye

3. Mental functioning, Attainment at School:

- whether there were any difficulties at School (according to the national special education

  needs code of practice framework; www.education.gov.uk)

 4. Sphincter function

- frequency of abnormal non age-related bedwetting/soiling

5. Specific daily and other neurological functioning and symptoms:

- fatigue affecting activities of daily living

- presence of symptoms of depression requiring further psychological support

- presence of seizures

- other neurological: brainstem; sensory problems.

The Expanded Disability Status Scale (EDSS) was also established(232). This is a tool method of quantifying disability in MS It is widely used in clinical trials and in the assessment of people with MS. The EDSS scale ranges from 0 to 10 in 0.5 unit increments that represent higher levels of disability. EDSS steps 1.0 to 4.5 refer to people who are able to walk without any aid and is based on measures of impairment in neurological functional systems as above. Each functional system is scored on a scale of 0 (no disability) to 5 or 6 (more severe disability). EDSS steps 5.0 to 9.5 are defined by the impairment to walking.

Table 35: Expanded Disability Status Scale (EDSS)

Score	Description
1.0	No disability, minimal signs in one Functional System
1.5	No disability, minimal signs in more than one Functional System
2.0	Minimal disability in one Functional System
2.5	Mild disability in one FUNCTIONAL SYSTEM or minimal disability in two Functional Systems
3.0	Moderate disability in one Functional System, or mild disability in three or four Functional Systems. No impairment to walking
3.5	Moderate disability in one Functional System and more than minimal disability in several others. No impairment to walking
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m
6.0	Requires a walking aid - cane, crutch, etc - to walk about 100m with or without resting
6.5	Requires two walking aids - pair of canes, crutches, etc - to walk about 20m without resting
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorised wheelchair
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow

Statistical Analysis

Descriptive statistics were used to summarise the key components of the dataset. Univariate associations between potential prognostics factors and potential confounders and second demyelinating episode within 12 months of a CIS (diagnosis of MS within 12 months of the first episode) will be described. Parametric or non-parametric statistical tests (Kruskal Wallis tests) were used for continuous distributions as appropriate given normality and χ^2 or Fisher's exact tests for nominal data. These associations were further explored in a logistic regression model (see below for detail) that allowed for control of confounding factors. Statistical analysis was performed using PASW Statistics for Windows version 17·0 (© SPSS, Inc., 2009, Chicago, IL, www.spss.com) and the openepi software (version 2·3·1, www.openepi.com).(201)

The following statistics are also presented for the various proposed diagnostic tests (236-240):

- Sensitivity- probability that the index test result will be positive in a diseased case.

- Specificity- probability that the index test result will be negative in a non-diseased case.

- Positive predictive value- probability that a case with a positive index test result is diseased.

- Negative predictive value-probability that a case with a negative index test result is non-diseased.

- Positive likelihood ratio- describes how many times more likely positive index test results were in the diseased group compared to the non-diseased group.

- Negative likelihood ratio describes how many times less likely negative index test results were in the diseased group compared to the non-diseased group.

Case Report form return

Table 36 below shows that a total of 90 out of 125 case report forms (72%) were returned (as of 28/05/2012). There were no differences between percentage number of ADEM, ON, TM, and CIS-other cases as compared to the original incident cohort described in chapter 2.4 (Chi squared= 4.409 with 3 degrees of freedom; two-tailed p value= 0.22). There may be a selection bias, towards cases returned being those with a clinical relapse, however, the occurrence of a clinical relapse did not influence the return of a case report form (as may have been expected). ADEM and TM cases had the highest case report return rates but the lowest clinical relapse rates.

Table 36: Outcome data follow up obtained

Expert classification	Follow up Obtained			Clinical Relapse in those with outcome obtained- n (% of cases with follow up)
	Yes	No	% data obtained	
ADEM (n=40)	32	8	80%	2 (6%)
ON (n=31)	17	14	55%	4 (24%)
TM (n=25)	20	5	80%	5 (20%)
CIS-other (n=27)	19	8	70%	11 (58%)
NMO (n=2)	2	0	100%	2 (100%)
Outcome (n=125)	90	35	72%	24 (27%)

Outcome- relapse and MS diagnosis

Table 37 below details the final one year outcomes for all cases. Out of the 90 cases with a reported outcome, one case died, 24(27%) had a clinical relapse; hence a minimum of 19.2% (24/125) had a clinical relapse. A total of 23 cases fulfilled IPMSSG multiple sclerosis diagnostic criteria (18 having two CIS relapses, and 5 having an initial CIS attack and then fulfilling the stringent McDonald 2001 MS MRI criteria for space and time). One ADEM case died in Hospital (see chapter 2.4). Two thirds of cases remained monophasic at one year follow up. Three cases had a non-MS clinical relapse and thee had a neuromyelitis optica relapse.

I am reporting both the minimum percentage based on the total cohort (n=125) as well as the percentage of responders (n=90). The fourth column represents the minimum percentage (and associated confidence intervals) of the described outcome. It is likely that the true value lies in between both values (%responders and minimum %).

Table 37: Outcome at one year following a first episode ADS.

Outcome	Count	% of responders [out of n=90](and 95% CI)*	Minimum % (and 95% CI)* based on n=125 cases
Multiple Sclerosis as per IPMSSG: CIS Clinical Relapse (n=18) <u>OR</u> new lesions on follow up MRI scan & fulfilling IPMSSG Multiple Sclerosis criteria-stringent McDonald 2001 MS MRI criteria for space and time (n=5)	23	25.6% (16.9-35.8%)	18.4 % (12.0-26.3%)
Relapse non-Multiple Sclerosis	3	3.3% (0.70-9.4%)	2.4 % (0.5-6.9%)
Neuromyelitis Optica Relapse	3	3.3% (0.70-9.4%)	2.4% (0.5-6.9%)
Death	1	1.1% (0.03%-6.0%)	0.8 % (0.02%-4.4%)
Monophasic illness (i.e. no relapse	60	66.67% (56.0-76.3%)	48.0% (39.0-57.1%)
No follow up	35	N/A	28.0% (20.3-36.7%)
Total	125		

Confidence intervals based on Exact method for proportions

Clinical Phenotype, relapses and MS Diagnosis

All cases fulfilling IPMSSSG criteria for MS diagnosed had a CIS as an initial presentation (Table 38 below). Of those with clinical relapses that did not receive an MS diagnosis (6/24) at one year follow up:

- 2 cases initially presented as NMO and had further relapses: transverse myelitis and optic neuritis.

- 1 case initially presented with TM, and the diagnosis changed from TM to NMO as the case had relapsed with optic neuritis and had longitudinally extensive transverse myelitis.

- 1 case initially presented with TM and had another transverse myelitis relapse (aquaporin-4 antibody negative) with a normal MRI brain (i.e. no asymptomatic T2 lesions).

- 2 cases initially presented with ADEM and had 2 further ADEM relapses.

11/43 (33%) monofocal cases developed MS, whilst 12/13 (92%) multifocal cases developed MS (Fisher's exact p<0.001). If multifocal CIS presentation is considered a predictive marker at one year follow up for MS diagnosis: Sensitivity= 52.2% (33.0, 70.8%); Specificity= 97.0% (84.7, 99.5%); Positive Predictive Value= 92.3% (66.7, 98.6%); Negative Predictive Value= 74.4% (59.8, 85.1%).

Cases presenting with monofocal with no asymptomatic MRI lesions were statistically less likely to develop MS at one year compared to: vs monofocal ≥ 1 asymptomatic lesion; & also compared to multifocal ≥ 1 asymptomatic lesion. There were no multifocal changes with no asymptomatic lesions (there were n=2 in the original incidence cohort).

Table 38: (A) Presenting phenotype as classified by the expert panel at onset of demyelination and corresponding MS outcome (B) All CI|S by detailed clinical (monofocal vs multifocal) and MRI phenotype (presence or absence of asymptomatic lesion)

				Multiple	Sclerosis		Significance For MS diagnosis at one year
				outcome			
			Non MS relapse (n=6)	No (n=61); monophasic	Yes (n=23); MS	% contribution to MS diagnosis (column %)	
A. Expert panel classification (n=90)	ADEM (n=32) [row%]		2¶ [6.3%]	30 [93.7%]	0	0%	
	All CIS (n=56)	ON (n=17) [row%]	0	13 [76.5%]	4 [23.5%]	17.4%	p<0.001 (chi^2 15.9; df=2) *
		TM (n=20) [row%]	2** [10.0]	14 [80.0%]	4 [20.0%]	17.4%	
		CIS- other (n=19) [row%]	0	4 [21.1%]	15 [78.9%]	65.2%	
	NMO (n=2) [row%]		2 [100%]	0	0	0%	
	monofocal no asymptomatic (n=28)		-	26 [92.9%]	2 [7.1%]	8.7%	
B. All CIS clinical (monofocal vs multifocal) and MRI classification (≥1 asymptomatic lesions) (n=56)	monofocal ≥ 1 asymptomatic lesion (n=15)		-	6 [30.0%]	9 [60.0%]	39.1%	p= 0.09 ¥ / p< 0.001 §
	multifocal ≥1 asymptomatic (n=12)		-	1 [8.3%]	11 [91.7%]	47.8%	
	radiologically isolated with ≥ 1 asymptomatic lesion (n=1)		-	0	1 [100%]	4.3%	

*ON vs TM vs CIS
¥ Fisher's exact; monofocal ≥ 1 asymptomatic lesion vs multifocal ≥ 1 asymptomatic lesion
¶ 2 MDEM (multiphasic acute disseminated encephalomyelitis) relapses
§ Fisher's exact; i. monofocal no asymptomatic vs monofocal ≥ 1 asymptomatic lesion &
ii. monofocal no asymptomatic vs multifocal ≥ 1 asymptomatic lesion
**One child's diagnosis changed from TM to NMO as the case had relapsed with optic neuritis and had longitudinally extensive transverse myelitis. Another child had another transverse myelitis relapse (aquaporin-4 antibody negative).

Details of CIS presenting phenotype, CIS type and Multiple Sclerosis diagnosis at one year are described in Table 39.

 Of children, with CIS:

All 4 ON cases who developed MS had ≥1 asymptomatic brain lesion

Of TM cases developing MS, 3/4 had had ≥1 asymptomatic brain lesion

Of monofocal other CIS cases developing MS, 2/3 had ≥1 asymptomatic brain lesion

Table 39: CIS presenting phenotype, CIS type and Multiple Sclerosis diagnosis at one year

CNS site clinical presentation	CIS phenotype	MRI brain	Multiple Sclerosis	
			No	Yes
MONO-FOCAL (n=43)	ON (n=17)	≥ 1 asymptomatic lesion	1	4
		no asymptomatic	12	0
	TM (n=20)	≥ 1 asymptomatic lesion	4	3
		no asymptomatic	12	1
	Other CIS (n=6)	monofocal ≥1 asymptomatic lesion	1	2
		monofocal no asymptomatic	2	1
Total			**32**	**11**
MULTI-FOCAL (n=13)	Other CIS (n=13)	multifocal ≥1 asymptomatic	1	11
		multifocal no asymptomatic	0	0
Total			**1**	**11**
radiologically isolated			0	1

On univariate analysis, Children who at first presentation of their CIS were older, and non-white (Table 40) were more at risk of developing MS compared to younger children or those of white ethnicity. Although females were more likely to receive a diagnosis of MS, this trend did not reach statistical significance. The duration of symptoms before presentation, and deprivation indices also did not influence MS diagnosis.

Table 40: Demographics and MS diagnosis

	Multiple Sclerosis		Significance (T-test/ Chi^2/ Fisher's exact)
	No (n=67)	Yes (n=23)	
Median Age at Presentation in years (range)	8.0 (1.3-15.9)	14.0 (9.5-15.0)	p<0.001
Sex (Male n=43: Female n=47) and %	35:32 (52%: 48%)	8:15 (35%: 65%)	p=0.15
White(n=67): non-white(n=22)	56:11 (84%:16%)	14:8 (64%: 36%)	p=0.048 risk ratio= 2.1 (95%CI:1.0-4.1)
Time from presentation to admission on initial presentation > 1 week	6/67 (9%:91%)	4/23 (15%: 85%)	p=0.27
Living in the most 20% deprived districts	19/58 (33%)	8/21 (38%)	p=0.66

Kruskal Wallis

CSF oligoclonal bands

Table 41, Table 42 and Table 43 demonstrate: CSF oligoclonal bands results at disease onset; CSF oligoclonal bands positivity and MS outcome; and value of CSF oligoclonal bands at disease onset for prediction of MS outcome.

In children with an outcome available who had a lumbar puncture done at initial presentation (55/90; 61%), 20 had positive CSF oligoclonal bands (20/55- 36%). Of those 16/17 (94%) with an eventual diagnosis of MS had positive CSF oligoclonal bands, whilst 4/38 (11%) with a monophasic illness had positive oligoclonal bands. There was a trend towards more children with CIS compared to ADEM cases having more CSF oligoclonal bands tested, probably as a result of the need to inform prognostication for future MS diagnosis.

Table 41: CSF oligoclonal bands results at disease onset

Expert panel classification	CSF oligoclonal bands		
	Done		Not done
	Positive	Negative	
ADEM (n=40)	2/20 (10%)	18/20 (90%)	20/40 (50%)
ON (n=31)	6/19 (32%)	13/19 (68%)	12/31 (39%)
TM (n=25)	5/18 (28%)	13/18 (72%)	7/25 (28%)
CIS (n=27)	11/16 (69%)	5/16 (31%)	11/27 (41%)
NMO (n=2)	0/1	1/1 (100%)	1/2 (50%)
Total	24/74 (32%)	50/74 (68%)	51/125 (41%)
Multiple Sclerosis as an outcome (n=24)where follow is obtained (out of n=90)	16/20 (80%)	1/35 (3%)	7/24 (29%)

Table 42: CSF oligoclonal bands positivity and MS outcome

	Multiple Sclerosis outcome		Significance* For MS diagnosis at 1 year
	No (n=61); monophasic	Yes (n=23); MS	
CSF oligoclonal bands positive	4/38 (11%)	16/17 (94%)	p<0.001

Table 43: Value of CSF oligoclonal bands at disease onset for prediction of MS outcome

Parameter	Estimate	Lower - Upper 95% CIs
Sensitivity	94.1%	(73.0, 99.0)
Specificity	89.5%	(75.9, 95.8)
Positive Predictive Value	80.0%	(58.4, 91.9)
Negative Predictive Value	97.1%	(85.5, 99.5)
Diagnostic Accuracy	90.9%	(80.4, 96.1)
Likelihood ratio of a Positive Test	8.9	(5.4 - 14.7)
Likelihood ratio of a Negative Test	0.066	(0.0092 - 0.47)
Cohen's kappa (Unweighted)	0.80	(0.54 - 1.06)

MRI predictors and Sensitivity and Specificity of MRI parameters for Multiple Sclerosis Diagnosis

Table 45 reports on the prognostic performance of the:

-   McDonald 2001 and 20010 (Table 44) pace criteria at first CIS presentation for MS diagnosis at one year (using IPMSSG diagnostic criteria as the reference standard).

-   McDonald 2010 MS criteria for space and time at first CIS presentation.

-   Verhey model for all CIS and ADEM presentations.

The Verhey model (for first presentation of ADEM and CIS) and the McDonald 2010 space and time criteria (for cases presenting with CIS and had gadolinium contrast) had the highest specificity. Only the McDonald 2010 space criteria for children presenting with CIS had sensitivity and specificity values above 80%.

I also the present the likelihood ratios for the MRI criteria/ predictor models.

Likelihood ratios are alternative statistics for summarising diagnostic accuracy, which have several particularly powerful properties that make them more useful clinically than other statistics, such as sensitivity and specificity. Positive and negative likelihood ratios are useful to understand the role of a test result in changing a clinician's estimate of the probability of disease in a patient (236-240).

LR it is the ratio of the probability of the specific test result in people who do have the disease to the probability in people who do no:

The further likelihood ratios are from 1 the stronger the evidence for the presence or absence of disease.

Likelihood ratios can be used to help adapt the results of a study to patients. To do this they make use of a mathematical relationship known as Bayes theorem that describes how a diagnostic finding changes our knowledge of the probability of abnormality.

Post-test odds for having disease= pretest odds x by the likelihood ratio.

A normogram can be used to help conversions between odds and probabilities.

In general, post-test probability, as estimated from the likelihood ratio and pre-test probability, is generally more accurate than if estimated from the positive predictive value of the test, if the tested individual has a different pre-test probability than what is the prevalence of that condition in the population.

Table 44: McDonald criteria definitions

	McDonald 2001 (87) as used in IPMSSG	**McDonald 2010 (22)**
DIS	3 or more of (a-d): a. ≥9 T2 lesions or 1 Gadolinium enhancing b. ≥3 periventricular lesion(s) c. ≥1 juxtacortical lesion(s) d. ≥ 1 infrantentorial brain lesion(s)***** **OR** the presence of 2 or more T2 lesions plus CSF oligoclonal bands	2 or more of: ≥1 periventricular ≥1 juxtacortical ≥1 infratentorial**§** ≥ 1 spinal cord**§**
DIT	1 Gadolinium enhancing lesion at least 3 months after CIS onset **OR** A new T2 lesion with reference to a prior scan obtained: >3 months after CIS onset	>1 new lesion when compared to a previous scan (irrespective of timing). **OR** presence of asymptomatic enhancing lesion and a non-enhancing T2 bright lesion on any one scan

DIS= dissemination in space; **DIT=**dissemination in time.

*In McDonald 2001 1 cord lesion can replace 1 brain lesion.

§ All lesions in symptomatic regions excluded in Brainstem and spinal cord syndromes.

Table 45: Specificity; Sensitivity; negative & positive predictive values; and likelihood ratios of various MRI parameters for multiple sclerosis diagnosis using the reference standard of IPMSSG diagnostic criteria.

MRI feature	Multiple Sclerosis		NPV *(100%-NPV= -ve post-test)* / **PPV** *(= +ve post-test probability & 95%CI)*	**Positive LR** [95%CI] / **Negative LR** [95% CI]
	No (n=67) [specificity; 95% confidence intervals]	Yes (n=23) [sensitivity; 95% confidence intervals]]		
McDonald Space criteria 2001 fulfilled for CIS patients	3/33 Specificity= 91%; [76-97%]	15/23 Sensitivity= 65%; [45-81%]	79%/ 83% [62-94]	7.2 [2.3-22] 0.38 [0.22-0.68]
Mc Donald Space criteria 2010 fulfilled for CIS patients	5/33 Specificity= 85%; [69-93%]	19/23 Sensitivity= 83%; [63-93%]	88%/ 79% [62-89]	5.5 [2.4-12] 0.20 [0.08-0.51]
Mc Donald Time 2010 space and time fulfilled for CIS **(at first scan, and with gadolinium contrast)**	1/26 Specificity= 96%; [81-99%]	7/12 Sensitivity= 58%; [32-81%]	83%/ 88% [49-98]	15.2 [2.1-110] 0.43 [0.22-0.85]
Verhey model for CIS & ADEM (1 black hole and 1 periventricular lesion)	2/66 Specificity= 97%; [90-99%]	9/23 Sensitivity= 39%; [22-59%]	82%/ 82% [51-95]	12.9 [3.0-55] 0.63 [0.45-0.87]
McDonald 2010 space criteria fulfilled for ADEM & CIS	20/67 Specificity= 70%; [58-%]	19/23 Sensitivity= 83%; [63-93%]	92%/ 49% [39-59]	2.8 [1.8-4.2] 0.25 [0.10-0.51]

LR: likelihood ratio

Multiple Sclerosis risk & Univariate analysis of MRI features

In Table 46, I explore univariate associations between MRI parameter and multiple sclerosis diagnosis within 12 months of a first demyelinating episode. Many MRI features could be associated with MS as an outcome. The following parameters reached significance (p<0.05) values:

- MRI abnormal

- McDonald 2010 space criteria fulfilled (including for ADEM & CIS cases)

- Verhey Prognostic Model criteria fulfilled (including ADEM & CIS cases)

- Presence of Gadolinium enhancing lesions

- Presence of Black Holes

- Presence of MRI infratentorial lesion

- Presence of Corpus Callosum lesion

- Presence of Periventricular lesions

- Presence of Juxtacortical lesions

Table 46: Univariate associations between MRI parameter and multiple sclerosis diagnosis within 12 months for all presentations of demyelination

		Multiple Sclerosis			
		No	Yes		
		Count	Count	Significance *	Risk Ratio (95% CI)
MRI abnormal		42/66 (64%)	22/23 (96%)	**p=0.003**	8.6 (1.2-60.6)
McDonald 2010 space criteria fulfilled for ADEM & CIS		20/67 (30%)	19/23 (83%)	**p<0.001**	6.2 (2.3-16.8)
Verhey Prognostic Model for ADEM & CIS		2/66	9/23	**p<0.001**	4.6 (2.6-7.9)
Gadolinium lesions		5/30 (17%)	7/12 (58%)	**p=0.01**	4.2 (1.5-11.8)
Black Holes		3/65 (5%)	9/23 (39%)	**p<0.001**	4.1 (2.3-7.2)
MRI infratentorial lesion		24/65 (37%)	14/23 (61%)	**p=0.046**	2.0 (1.0-4.2)
Poorly demarcated lesions		27/67 (40%)	6/23 (26%)	p=0.32	0.61 (0.27-1.4)
Cortical Grey		12/66 (185)	0/23 (0%)	p=0.1	n/a
Corpus Callosum		5/66 (8%)	12/23 (52%)	**p<0.001**	4.6 (2.5-8.6)
Deep grey nuclei		19/66 (29%)	2/23 (9%)	p=0.084	0.3 (0.8-1.2)
Periventricular lesions	0 lesions	54 (82%)	4 (17%)	**p<0.001** §	8.9 (3.3-23.8)
	1-4 lesions	6	6		
	=> 5lesions	6	13		
Juxtacortical lesions	0 lesions	40 (61%)	7 (30%)	**p=0.05** §	2.4 (1.1-5.4)
	1-4 lesions	9	4		
	5-9 lesions	10	5		
	>10 lesions	7	7		
Spinal lesions present		24/36 (67%)	9/10 (90%)	p=0.07	3.5 (0.5-25.2)
Spinal lesions ≥3segments		20/36 (56%)	3/10 (30%)	p=0.15	0.4 (0.1-1.5)

* Fisher's exact; except where §: Kruskal- Wallis

Logistic Regression

Table 47 describes the binary logistic regression model and model summary.

Variables used as predictors

Proposed candidate predictors which have previously been reported as prognostic (and were significant [p<0.05] on univariate analysis) were used. Oligoclonal bands were not used as not all cases had CSF testing (55/90 of those with an outcome-61%). The following 8 variables were derived from the dataset and investigated as predictors in the dataset where the outcome was known (n=90):

- Age, and ethnicity

- MRI brain abnormal

- MRI features:

    o Black Hole(s) present

    o MRI infratentorial lesion present

    o Corpus Callosum lesion present

    o Periventricular lesion present

    o Juxtacortical lesion present

Outcomes measured

For the purposes of this study, multiple sclerosis diagnosis as per the 2007 IPMSSG definitions were used.

Statistical methods

Statistical analysis was carried out with SPSS version 17.0. For the binary logistic regression (for multiple sclerosis diagnosis), a backward elimination approach was used for the logistic

regression, with entry at p value of <0.01 and removal at p<0.05. Performance of the model

was assessed with a classification plot and table, Hosmer and Lemeshow test, ROC analysis,

Cox & Snell R square and, Nagelkerke R Square. The dataset was not randomly split to

conduct an internal validation due to the relatively small numbers (for example by assessing

the predictive accuracy of the model on a second portion of the dataset) and therefore

remains exploratory.

Figure 16: ROC curve analysis illustrates the ROC curve analysis; while Table 48 describes the

area under ROC curve, test results: predicted probability and selected consecutive

coordinates of the ROC Curve

Table 47: Binary logistic regression model and model summary

Variables	B	Wald Chi^2	Significance	OR	95% C.I.for EXP(B) Lower	Upper
Age At Presentation	0.537	11.2	p=0.001	1.71	1.25	2.34
Periventricular lesion present	4.008	17.8	p<0.001	55.1	8.54	354.9
Constant	-9.4	16.269	p<0.001	<0.001		

Performance Test	value
-2 Log likelihood	38.622
Cox & Snell	0.498
Nagelkerke R Square	0.731
Hosmer and Lemeshow Test (chi^2, significance) Df=7	4.595; p=0.709

The predicted risk or probability of MS diagnosis at one year can be calculated as $1/(1+e^{-risk\ score})$ where the risk score = -9.4 + (0.537x age) + (4.008 x presence of periventricular lesion [1=yes]).

Figure 16: ROC curve analysis
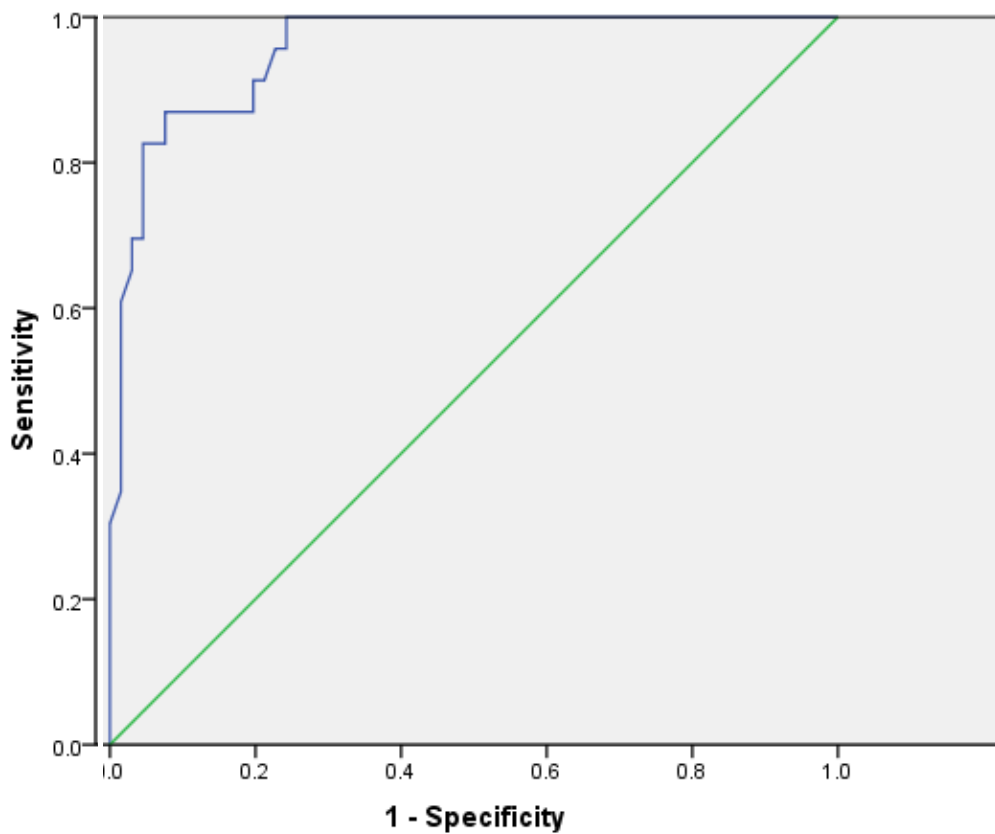
Table 48: Area under ROC curve, test results: predicted probability and selected consecutive coordinates of the ROC Curve

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.956	.020	<0.001	0.916	0.995
a. Under the nonparametric assumption				
b. Null hypothesis: true area = 0.5				
Test Result Variable(s):Predicted probability				
Positive if Greater Than or Equal To		Sensitivity	1 - Specificity	
0.1633706		0.870	0.152	
0.1936447		0.870	0.136	
0.2356800		**0.870**	**0.106**	
0.2746848		**0.870**	**0.076**	
0.2855053		**0.826**	**0.076**	
0.2947609		**0.826**	**0.061**	
0.3599139		**0.826**	**0.045**	
0.4278547		0.783	0.045	
0.4811851		0.739	0.045	

A predicted probability ≥0.27 yields a sensitivity=87.0% and specificity =92.4%.

Classification and regression tree analysis (CART)

The CART algorithm is based on classification and regression trees devised by Breiman et al (241). A CART tree is a binary decision tree that is constructed by splitting a node into two child nodes repeatedly, beginning with the root node that contains the whole learning sample. It is likely to provide a useful model for clinicians to aid in decision making. A tree is grown starting from the root node by repeatedly using the following steps on each node. For each continuous and ordinal predictor, its values are sorted from the smallest to the largest. The best split point is the one that maximize the splitting criterion the most when the node is split according to it. The definition of splitting criterion is in a later section. Figure 17 illustrates the Decision Tree for multiple sclerosis outcome at 1 year (N=90); whilst Table 49 shows the classification table based on decision tree and CHAID method of tree growing.

Figure 17: Decision Tree for multiple sclerosis outcome at 1 year (N=90)
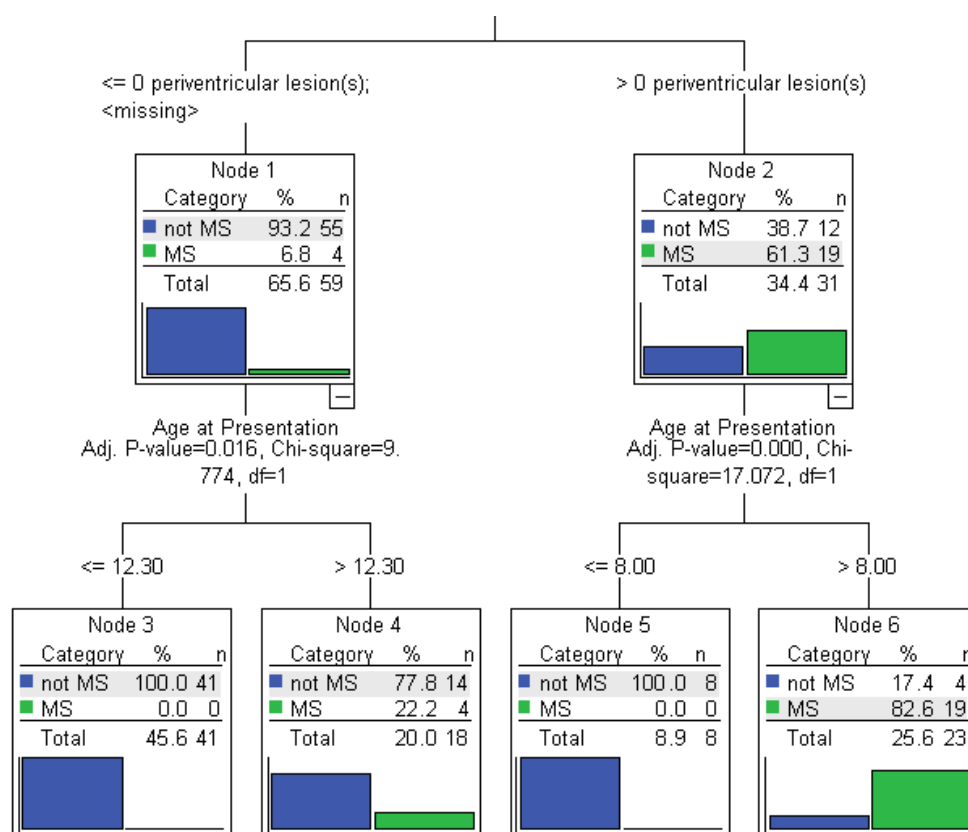
Table footnote:
Node = 1; prediction = not MS probability = 0.932203
Node = 2; prediction = MS probability = 0.612903

Node = 3; not MS probability = 1.000000 (less than 12.3 years old & no periventricular lesion)
Node = 4; not MS probability = 0.777778 (more than 12.3 years old & no periventricular lesion)
Node = 5; not MS probability = 1.000000 (less than 8 years old & ≥1 periventricular lesion)
Node = 6; MS probability = 0.826087 (more than 8 years old & ≥1 periventricular lesion)

Table 49: Classification table based on decision tree and CHAID method of tree growing

Classification			
Observed	Predicted		
	not MS	MS	Percent Correct
not MS	63	4	94.0%
MS	4	19	82.6%
Overall Percentage	74.4%	25.6%	91.1%

Risk estimate= 0.089 (standard error=0.30)

Disability outcomes

A total of 39% of children had an EDSS of 2.0 or worse (minimum 32/125 or 23.2% of entire study cohort), that is a least minimal disability in one functional system or more (Table 50). The majority of ADEM and ON cases had an EDSS of less than 2.0 (75% and 85% respectively) at one year outcome. Also, at one year, 10% of the outcome group had an EDSS of 6.0 or worse, requiring a walking aid of for the majority of the time (minimum 8/125 or 6.4% of entire study cohort). The majority of these children with severe disability presented with a transverse myelitis phenotype (6/8).

Fatigue was reported to clinicians as affecting 19% of children with a first demyelinating at the one year outcome. Multiple sclerosis patients were most commonly reported fatigue with 9/17 being affected (53%). Poor visual recovery was reported in 10%, and all 3 patients with NMO (of which 2/3 were aquaporin-4 antibody positive) affected. Sphincter disturbance at one year was reported in 11% with the majority being TM sufferers. School attainment was affected in 10%, with 5/8 affected patients presenting with ADEM. Depressive symptoms were also spread across the different phenotypes with 13% being affected.

Table 50: Summary of disability outcomes by presenting phenotype, where all disability outcomes reported (83/90)

		MS (n=19)	ADEM (n=28)	ON (n=13)	TM (n=14)	CIS-other (n=3)	Relapse-non MS (n=3)	NMO (n=3)	Total (n=83)
Poor visual recovery in at least 1 eye		1	1	2	0	0	1	3	8 (10%)
Sphincter disturbance		0	2	0	6	0	0	1	9 (11%)
School attainment		1	5	0	0	1	1	0	8 (10%)
Fatigue		7	4	0	4	0	0	1	16 (19%)
Focal symptomatic seizures		0	2	0	0	0	0	1	3 (4%)
Depression symptoms		3	3	0	2	2	0	1	11 (13%)
EDSS disability	0/1.0	11 (58%)	21 (75%)	11 (85%)	5 (35%)	2 (67%)	1 (33%)	0 (0%)	51 (61%)
	2	3	3	0	2	1	0	1	10 (12%)
	2.5	1	0	0	0	0	0	0	1 (1%)
	3	3	2	2	1	0	0	0	8 (10%)
	4	1	2	0	0	0	0	2	5 (6%)
	6	0	0	0	3	0	2	0	5 (6%)
	6.5	0	0	0	1	0	0	0	1 (1%)
	7	0	0	0	2	0	0	0	2 (2%)

Discussion and Conclusions

Follow-up case return after initial ascertainment

Outcome data return was available for the majority of cases (72%), however, case report return was lowest for optic neuritis (55%) cases compared to the other acquired demyelinating syndromes. This may be due to a lower rate of clinical follow up for these cases. This however if anything, should not bias the analysis towards higher MS percentage outcomes, given that syndromes typically associated with lowest MS rates had the highest case return rate (ADEM; 80% and TM 80%). In addition, cases with the highest case return, also had the lowest clinical relapse rate after one year (ADEM 6%; TM 20%) hence reducing the likelihood that case return was due to cases more likely to have a relapse.

It is important to acknowledge that some of the children currently classified as being monophasic demyelination may eventually be reclassified as having multiple sclerosis at a 2 year or longer follow up, however, published data to date consistently reports a short interval between the first attack and a relapse (typically <12 months) in paediatric multiple sclerosis [13-16]. This fact reduces the likelihood of a misclassification of demyelination outcome in this study. In addition, MRI brain scans are now widely and routinely utilised, hence increasing the chance of diagnosis by MRI criteria for multiple sclerosis before a clinical attack occurs. Also, throughout this chapter, I report the minimum percentage of the outcome (relapse, disability outcomes) based on the entire cohort (where appropriate) of the described outcome.

The methodological advantages of this surveillance study, is that it prospectively reports detailed outcomes (with MRI review) from children with first onset demyelination ascertained from all clinicians seeing cases with paediatric demyelination in the British Isles. Asking all secondary care paediatricians and ophthalmologists (as well as tertiary care specialists) to report cases potentially has the advantage of seeing 'milder' cases which may not have been clinically referred to tertiary centres. However, children who have a relapse are frequently referred to a paediatric neurologist (typically tertiary care for another opinion). It is worth considering also that the 100% recruitment rate of reported cases was only made possible after stringent ethical reviews by an NHS multicentre ethics board, and the NIGB ethics boards to collect data without patient consent. Annual reports and progress were provided to both bodies (as well as to the BPSU, BOSU, and the MS Society) to ensure good progress, adherence to ethical and to system level security policies. Patient confidentiality remained a top-priority as described in chapter 2.1.

Outcomes: relapse and MS diagnosis

Just over one quarter of this British Isles cohort where outcome was available (minimum 18.4% of entire cohort [n=24/125]) satisfied IPMSSG criteria for MS. This is comparable to a large prospective multicentre cohort Canadian study, with a reported rate of 21% within one year (23, 96). In addition, six other children had a clinical relapse within one year after first presentation: three with a neuromyelitis optica relapse; 2 with MDEM; and one TM There was also one death (chapter 2.4) after a presentation with ADEM. Cumulatively, this means that a minimum of 24% (30/90; 33% of those with a reported outcome) had an adverse outcome (MS diagnosis, relapse, death). These outcome data confirm that approximately one third of cases of demyelination have an adverse outcome, and that a one year follow up

is sufficient to consider the efficacy of possible future interventions at the onset of the acquired demyelinating syndrome.

Clinical Phenotype, relapses and MS Diagnosis

All cases diagnosed with MS had CIS as the initial presentation, confirming results from recent reports in the literature [16]. The presence of encephalopathy, hence appears to be a useful negative predictor for MS diagnosis, and useful in diagnosis ADEM in children with multifocal presentation. However, this term has often caused controversy in the literature (20) as it is a loosely defined clinical term and is somewhat subjective. Also the fact that a significant number of patients were reclassified by the expert panel from ADEM to CIS in the surveillance incidence study (chapter 2.4) confirms the difficulty of classifying ADEM from polyfocal CIS based only on clinical parameters. Hence, additional supportive features, such as conventional MRI measures, would be particularly helpful.

The majority of cases meeting IPMSSG MS criteria presented with other-CIS syndromes (15/23 [65%]) at initial onset, whilst 4 initially presented with ON and 4 with TM. Of all CIS types, the majority had asymptomatic MRI brain lesions (20/23 – 87%). This confirms adult and paediatric observations that the presence of symptomatic brain lesions are an important predictor of MS development (40). Another way to describe these cases is as 'CIS suggestive of MS' as in the recent emerging adult literature (88, 242-244). A total of 11/23 (47%) cases diagnosed with MS presented with a monofocal syndrome, 11/23 presented with a multifocal syndrome, and 1 presented with a radiologically isolated syndrome. This ratio of an equal number monophasic and multiphasic cases is different than a retrospective Dutch

study (n=117) where 43% of monophasic CIS cases vs 21% polyfocal CIS cases developed MS (20). It may be that, in this study, the consistent classification of multifocal CIS cases with encephalopathy to ADEM has resulted in the observed ratios. Three recent studies applying the 2007 IPMSSG definitions of ADEM (2 single centre cohort studies; and one large Canadian multicentre prospective cohort study) have shown an MS conversion rate of less than 10% (13, 14, 96). It hence appears that encephalopathy at presentation is a negative predictor of MS, however, long term follow up (as in the PUDDLS study I set up, see chapter 4.1, (210)) is still needed to clarify, which cases are actually MDEM, MS or other recurrent forms of demyelination. Until reliable biomarkers of subgroups of demyelination are established in the future, clinical epidemiology will continue to provide valuable information about subgroups in the likely heterogeneous acquired demyelinating syndromes and their relapsing forms. Once biomarkers are proposed, as in the case of neuromyelitis optica (aquaporin 4 antibody), clinical-MRI phenotyping will play an important part in validating these potential biomarkers(245).

Only two children with CIS presentations and no other asymptomatic brain lesions developed MS (one with optic neuritis and one with a brain stem syndrome). All other CIS presentations who later were confirmed as having MS had asymptomatic MRI brain lesions. Multifocal CIS presentations had a higher MS conversion rate for MS at one year compared to children presenting with monofocal presentations (sensitivity 52% and specificity 97%). Overall, children with clinical presentations consistent with a clinically isolated syndrome, and have MRI brain silent lesions are at high risk of developing MS. It is important to bear in mind that, these cases were referred by the clinician following inclusion criteria as to what

constitutes a paediatric acquired demyelinating syndrome (see chapter 2.1) and after expert panel exclusion of cases (n=19) which were other conditions. These results regarding the prognostic risk factors at demyelination onset confirm recent trends reported in the literature (23, 96, 246, 247).

Demographics and MS diagnosis

The ratio of females to males diagnosed with MS reached 1.9:1. Although this did not reach statistical significant numbers, this ratio is consistent with recent paediatric as well as adult reported literature (3, 4, 23). This observed sex ratio, adds weight that it is likely that events (e.g. environmental exposures) occurring at or even before puberty onset that. Also consistent with recently reported studies, children with MS were significantly older at presentation compared to those with monophasic ADS (24). In addition, non-white children with a first episode of demyelination were more at risk of an MS diagnosis at one year (risk ratio 2.1).

CSF oligoclonal bands

As this is a clinical pragmatic study, and lumbar punctures were not done routinely as part of research, a relatively limited number of CSF information was available. Although there was a trend towards more children with ADEM having a lumbar puncture as compared to CIS (50% vs 63% p=0.35), this did not explain these findings.

MRI predictors parameters for Multiple Sclerosis Diagnosis

The McDonald Space criteria 2001, as used by the IPMSSG, fulfilled for CIS patients had a high specificity (91%) but a low sensitivity (65%). The Verhey model (for first presentation of

ADEM and CIS) and the McDonald 2010 space and time criteria (for cases presenting with CIS and had gadolinium contrast) had the highest specificity. Only the McDonald 2010 space criteria for children presenting with CIS had sensitivity and specificity values above 80%. My results are consistent with a recent retrospective MRI Austrian and German study of 52 children with CIS; the 2010 McDonald dissemination in space criteria were also more sensitive (85% versus 74%) but less specific (80% versus 100%) compared to the Barkhof criteria for space. The 2010 McDonald criteria for dissemination in space and time also had a high specificity (93%) (248).

With regards to MRI parameters for all children presenting with an acquired demyelinating syndrome, the following had a significant association with MS diagnosis (listed from highest to lowest risk ratio):

Periventricular

MRI abnormal

McDonald 2010 space criteria fulfilled for ADEM & CIS

Corpus Callosum

Gadolinium lesions

Black Holes

Verhey or MacDonald 2010 Space + Time fulfilled for ADEM & CIS

Juxtacortical

MRI infratentorial lesion

Interestingly, also similar to the recent Austrian/ German study, the Inclusion of the spinal cord did not increase the accuracy of the McDonald criteria. (248).

Disability and Functional outcomes

There is a paucity of data on the neurodisability and functional outcomes following paediatric acquired demyelinating syndromes. In this study more than one in three children has at least minimal disability in one functional system or more. The majority of ADEM and ON cases had a good functional recovery. One in ten children however suffered a severe disability at one year with an EDSS of 6.0 or worse, requiring a walking aid of for the majority of the time. The majority of children with severe disability presented with a transverse myelitis phenotype (6/8).

As in adult MS where fatigue is a prominent feature, 1 in 5 children reported symptoms of fatigue at the one year outcome. Multiple sclerosis patients were most commonly reported fatigue. Importantly, poor visual recovery was reported in 1 in 10, and in all 3 patients with NMO. School attainment was affected in 1 in 10 children, hence highlighting the importance of participation and considering every day activities of daily living (191).

Conclusion & Clinical Implications

In children presenting with an acquired demyelinating syndrome, children with a CIS are more likely to have a clinical relapse than those with ADEM over the course of one year. This has important implications with regards monitoring and the requirement of repeating an MRI scan after an interval. Currently with the wide availability of MRI, an increasing number of children are having follow up scans. Internationally proposed criteria which help the clinician in predicting and diagnosing multiple sclerosis in childhood have been proposed which require validation. Table 51 summarises findings from the surveillance 1 year outcome findings relative to similar international contemporary cohorts.

Table 51: Characteristics of UK ADS cohort compared to similar international contemporary cohorts

	Thesis	Dutch cohort (249)	French cohort (15, 77)	Canadian Cohort (32, 98, 250)	USA cohort (33)
Study Design; Year	Active surveillance population 2012	Population/ prospective 2011	Population/ prospective 2003	Population/ prospective 2008	Retrospective; Southern California population 2010
Sample size	N=125				
Duration of follow up					
Age range					
Age of onset of first event (any)					
Age of onset of ADEM					
Age of onset of MS					
% ADEM with relapse					
% of CIS with MS diagnosis					
% patients <10 years at onset of MS					
% patients < 6 years at onset MS					
Time to first relapse					

The results in this chapter compare the IPMSSG (use McDonald 2001), the Verhey prognostic model, and also the latest version of the McDonald 2010 MRI criteria. AN important overarching assumption in this study is that these cases are indeed presenting with an initial inflammatory demyelinating event, as opposed to a 'mimicker.' I have already highlighted the wide differential diagnoses in chapter 2.7 and that in fact 19 cases were excluded as they did not represent an acquired demyelinating syndrome. This is an important factor to consider when drawing up guidelines for childhood multiple sclerosis, and relapsing inflammatory demyelinating diseases. The McDonald 2010 criteria have only been recommended for use in children presenting with CIS, and not ADEM. Children with ADEM have several features on initial presentation (as highlighted in chapter 2.4) that appear to distinguish them from polyfocal CIS. The presence of encephalopathy is by a definition a clinical requirement to distinguish between ADEM (presence of) and polyfocal CIS (absence of). The new McDonald 2010 criteria appear to have good overall specificity and sensitivity (over 80%) for children presenting with CIS. However, on univariate analysis there were other factors (besides MRI) that were important to take into account when predicting outcome such as age; and CSF oligoclonal bands. Previous international studies (this is the first study of its kind in the UK) have tended to focus on clinical features, MRI features and CSF oligoclonal bands in isolation. By combining these factors in a clinical algorithm, more accurate predictors could be devised. Interestingly, and consistent with other studies, MRI spine does not seem to be an important factor in predicting early MS progress, and hence this could save on follow up scan time, an important factor when scanning children who may require sedation.

This may be because it is unusual for MRI spine in children to show asymptomatic lesions, and in fact children presenting with myelitis usually have sign and hence have a spinal MRI.

The logistic regression and decision tree analysis both highlighted that age, and the presence of periventricular lesions on the MRI in **_all_** children presenting with acquired demyelinating syndromes are important predictors of childhood MS.

Prognostic indicators as highlighted will have to be externally validated in other populations, and there is an opportunity for this as the IPMSSG are already setting up a database to allow multinational collaborations and externally validating models. Importantly, CSF oligoclonal bands were not inserted in to models or decision tress as not all children had a lumbar puncture. On univariate analyses, CSF oligoclonal bands were very useful as a predictor test for MS development. In children presenting with possible demyelination, it may be that national guidelines are needed to mandate a protocol MRI and a lumbar puncture to be done at outset, or close to onset. However, this indeed may be difficult to apply, for example in a child who present with mild symptoms and who is already recovering.

Strengths of this work include that it is a large national interdisciplinary epidemiological study which uses multiple sources and two well established active surveillance units. Unique to this prospective population surveillance study is integrated detailed review of MRI images and investigative features combined with the robust application of International Paediatric Multiple Sclerosis Study Group (IPMSSG) consensus definitions by an expert panel (for inclusion, exclusion and differential diagnoses). This is study has applied the newly revised MS 2010 Macdonald diagnostic criteria for MRI in a population based series. This has implications for diagnostic work-up of these patients, potentially for therapeutics including

proposed clinical trials given that, to date, the European Medical Agency has approved nine

new MS drugs for study in the paediatric population.

CHAPTER 4: TOWARDS FUTURE LONGITUDINAL COHORT & BIOMARKER STUDIES, AND CLINICAL TRIALS

I will describe the set up of the Paediatric UK Demyelinating Disease Longitudinal Study (PUDDLS), a prospective multicentre longitudinal observational study, which will help to determine the natural history, predictors and clinical and patient centred outcomes of childhood acquired demyelinating syndromes.

To date, eight new MS drugs have been recommended for a Paediatric Investigation Plan, with earlier diagnosis increasing the eligible clinical trial population. There are no clinical trials in childhood ADS or in MS. I will hence discuss consideration in the design of trials in paediatric ADS and multiple sclerosis. Specifically I will illustrate this by:

(i) exploring how by using large phase adult 3 clinical trials can inform paediatric clinical trial design; (ii) calculating sample sizes for clinical trials by using published paediatric multiple sclerosis annualised relapse rates to calculate samples sizes for a clinical trial;

(3) exploring the potential design of a future transverse myelitis treatment clinical trial.

4.1 Multicentre cohort study setup and methodology for patient centred and clinical outcome measurement

INTRODUCTION

Although I have set up a national surveillance study with one year follow up (2.1 and 3.5), there is limited knowledge on detailed patient functional outcomes following childhood onset acquired demyelinating syndromes, I therefore established a prospective longitudinal cohort study. You will find the protocol detailing study aims, hypothesis, design and methods in *Appendix 4*. The Paediatric UK Demyelinating Disease Longitudinal Study (PUDDLS) is a prospective longitudinal observational study which aims to determine the natural history, predictors and outcomes of childhood acquired demyelinating syndromes. Here I will describe some of the consideration that needed to be addressed and reviewed for the protocol design and also in order to provide useful outcome measures, and to establish a biomarker resource for further hypothesis research.

ISSUES TO ADDRESS

The available literature on paediatric MS, is primarily limited to smaller case series and larger retrospective reviews of established adult MS populations (11, 26, 31, 39, 77, 83, 176, 221, 251-256). Evidence for differences in natural history of childhood onset MS(5) are also primarily derived from retrospective cohorts, as are studies linking environmental factors (EBV infections or Vitamin D deficiency) with possible MS development(257). In the following section I will address the following four issues:

1) **Recruitment & Follow up**

2) **Patient involvement**

3) **Biological biomarkers and genetic analysis**

4) **Patient reported outcome measurement.**

1) **Recruitment & Follow up**

In order to establish a large cohort in a rare disease and also longitudinally follow children up, treating neurologists will need to recruit affected children and from many tertiary centres from as many centres in England at first onset of the acquired demyelinating syndrome (Figure 18: PUDDLS Flowchart with link to epidemiological study). In contrast to the surveillance study described in Chapter 2.1, parents will need to provide consent (and children assented). Given the rarity of the disease, the recruitment period will need to extend beyond 3 years. In addition, in order to allow for the movement of patients and to avert the loss of follow up, patients will need to be requested to consent to be contacted in the future, directly or via the NHS Information Centre [Medical Research Information Service (MRIS)] and the NHS Central Register. In addition, patients will be consented to also be contacted by telephone interview as the clinician may have decided that clinic follow up was not necessary unless the patient has another event or relapse.. Finally, future international collaboration in this rare group of disorders is likely to be important and hence, establishing a dataset with key core information as per agreed published guidance ((12)) and definitions will be important.

The need for longitudinal follow up is important as the proposed international consensus definitions (12) for ADS are operational and require evaluation in prospectively followed up cohorts. Furthermore, MRI criteria used in adults to diagnose MS e.g. MRI McDonald criteria may not be valid in children (24, 91, 224). The utilisation of revised McDonald criteria (22) and others including the Verhey prognostic model (96) need to be validated in new cohorts. Although most children relapse within the first 2 years of after ADS onset, there may be a group of children who have more benign disease course or suffer a relapse many years after initial onset, and hence the need for longitudinal follow up.

Figure 18: PUDDLS Flowchart with link to epidemiological study
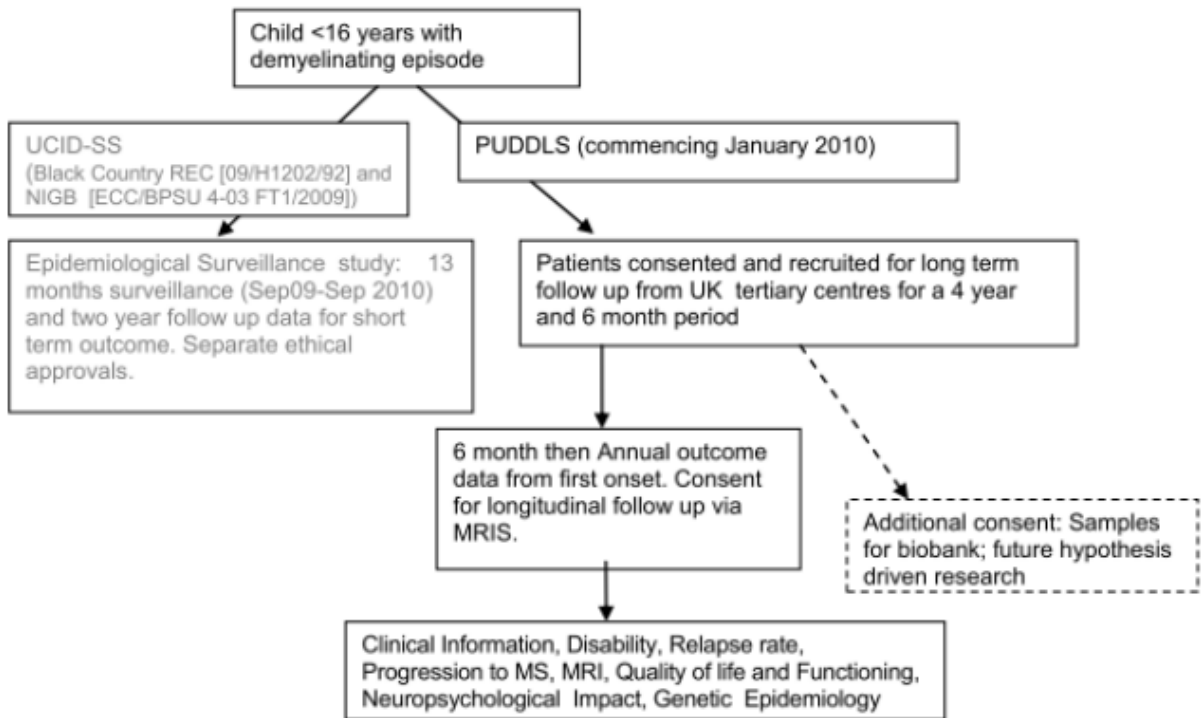
2)   **Patient involvement**

I have also recruited a lay representative from the MS Society in the study team to ensure that patient and family views are appropriately sought throughout the study. The lay representative has helped towards input into appropriate questionnaires to administer to children and their parents/guardians and also in design of the patient information leaflets.

3)   **Biological biomarkers and genetic analysis**

In line with adult based studies (258), there is no currently available biomarker that fulfils the criteria of a surrogate endpoint in MS in children. Current routine tests including CSF oligoclonal bands, lack sensitivity and specificity in individuals presenting with a first CNS inflammatory demyelinating event. Genetic epidemiology to date supports the dual role of "nature and nurture" in MS pathobiology(2). As such paediatric cohorts can also offer further valuable insights into the genetic and environmental interactions in the pathogenesis of MS. The corner stone of cohorts that are likely to be able to address complex disorders such as MS, depend on the availability of biological sample with comprehensive databases with clinical information (Figure 19) as well as genetic-environmental questionnaires.

Figure 19: The 5 major study themes are represented in flow the Figure below.
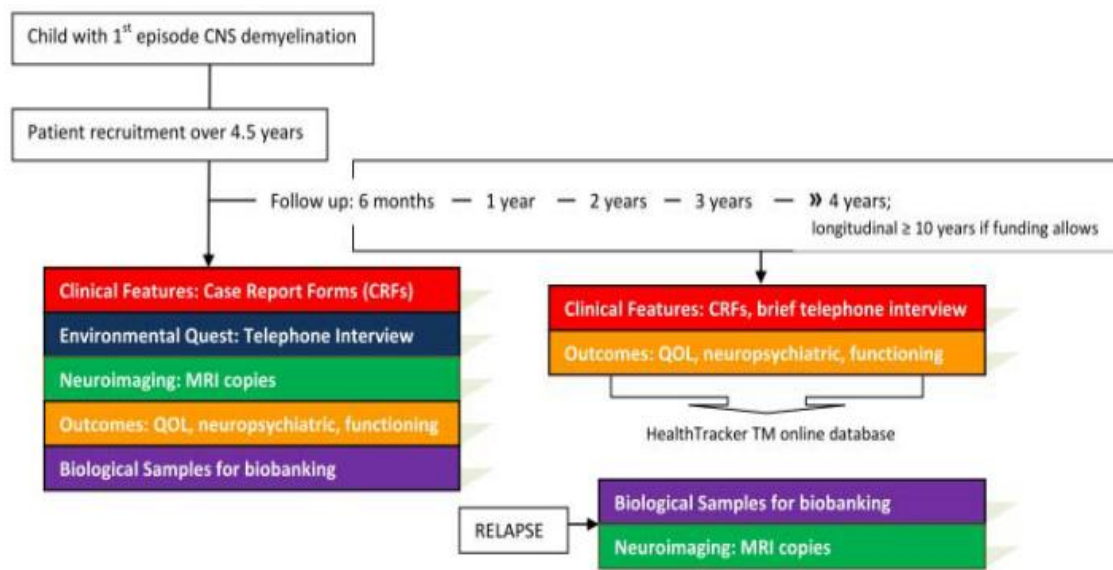
4) **Patient reported outcome measurement**

The determination of the patient reported outcome measurements are becoming increasingly important for the design of any future prevention or treatment trials. There is a need for a better understanding of long-term outcomes including quality of life, cognitive, adaptive behavioural and functional skills, neuropsychiatric symptoms, and treatment effects for children presenting with CNS inflammatory demyelination. I have hence designed a cohort study that ascertains patient and proxy reported generic and disease specific measures (Figure 20).

Figure 20: Data and Outcome Collection Schedule Summary

Data Collection/procedure	At recruitment	6 months After onset	Yearly after first event	Additionally at relapse (s)
Information leaflets & consent/assent	×Δ			
First episode performa (CRF) [Δ]	× Δ			
Follow up/ Relapse performa (CRF) [Δ]		× Δ	× Δ	
MRI copies	× Δ	× Δ		× Δ
Sample Collection for biobanking	×			×
*Pediatric Quality of Life Inventory TM and Multidimensional Fatigue and Scale (10 minutes)	☺ ♣	☺ ♣	☺ ♣	
* Profile Of Neuropsychiatric Symptoms (10 minutes)	☺ ♣	☺ ♣	☺ ♣	
*Adaptive Behavior Assessment System II; conceptual + social skills (10 minutes)	♣	♣	♣	
*MSIS-29 (5-10 minutes)	☺ ♣	☺ ♣	☺ ♣	
Cognitive games (10 minutes)	☺	☺	☺	
Brief outcome telephone interview: check if relapses occurred (10 minutes)		Δ ♣	Δ ♣	

*Health Tracker® online
- Environmental Questtionaire: Telephone Interview with parent/carer (30-45 minutes) will also take place once during the study period within 6 months after disease onset.

× Neurologist Collaborator/ PI   ☺ Child   ♣ Parent/Carer   Δ Research Nurse/Research Fellow

Acquired demyelinating syndromes (ADS) and whether monophasic or relapsing can result in impairments in: motor function; bladder and bowel function; vision; cognition; and mood. The ADS are a group of heterogeneous disorders, with unpredictable natural history and of low incidence. Additionally these conditions usually have complex, overlapping symptoms, and co-morbidities that are important to measure. Measuring outcomes in children with ADS hence provides significant challenges in every day practice and research. At the time of writing, however, there are no agreed systems that allow monitoring of all areas of potential change, and are able to monitor symptoms, impact on family life and individual children's quality of life and participation systematically. Measuring the impact of future therapies is hence challenging due to the additional barrier of a lack of nationally or internationally accepted core outcome measures. There is also the difficulty of using a multitude of paper based questionnaires (generic or disease specific) which are often labour intensive, not readily repeatable, and not designed to measure change.

Ideally inclusion criteria for outcome measures should include:

The ideal criteria to realise the study aims are:

1. Measures that encompass the framework developed by the World Health Organisation's International Classification of Functioning, Disability and Health (ICF). Measures should also reflect agreed definitions and standards.

2. Suitability for longitudinal assessment into adulthood.

3. Ease of administration and access for children, and families. Ideally allowing completion in child centred methods (including allowing self report) via secured internet access. Hence avoiding extra laborious paper based assessments to be sent by post, and

excessive Hospital visits. Parent reported (proxy completion) methods should also be available, with ideally good agreement with the child self report measures.

4. Brief and minimal response burden for children and families, whilst allowing rapid analysis by staff.

5. Normative data available for UK children

6. As well as being clinically useful for this study population, scientific robustness is an important consideration, specifically relating to the tool's psychometric properties: Reliability; Validity; Responsiveness; & Appropriateness

7. Measures should include:

   - Objective as well as subjective analysis

   - Generic and Disease Specific items

8. Measures should ideally be cross-culturally compatible.

Option of using Disease Specific Questionnaire based on already established adult tool

The lack of outcome tools in childhood ADS has been highlighted by the international paediatric demyelinating disease study group (166). There is a hence a need to consider the use of one or more disease specific measures previously designed for use in the adult population. In this case, these measures will require additional validation for use in children. There are however advantages to basing new measures of QoL for children on those previously developed for adults. These include: potential value in longitudinal studies where there is a need to determine changes in QoL across the life-span; and the opportunities to draw on established expertise of those working in adult disease specific QoL measures. It also costs less if some of the basic stages of item determination used in adult work can be assumed appropriate for use in children.

The disadvantages of this approach also need to be recognised. QoL is usually regarded as a multidimensional concept related to the ICF definitions of health proposed by the WHO (**Error! Reference source not found.**). In adapting adult QoL measures for children, a entral question relates to how well the domains assessed in adult measures are appropriate to assess QoL in children.

The traditional domains, including physical QoL may not have the same meaning for children as adults. In adult work, there is an emphasis on attainment of everyday routine activities which may not fully reflect the range of physical activities typical of normal children.

Adult measures may fail to tap the specific aspects of QoL that are important to the child. At the least, additional domains to tap autonomy, body image, cognitive skills and relationships with the family are needed. Failure to include these domains may limit understanding of the child in a social context and therefore does not provide a robust framework for the development of measures for children. Response scales, wording and format of adult measures may need modifying to account for children's cognitive and language skills.

To help address difficulties with administering questionnaires primarily designed for use in adults to children, I have chosen to use a novel biomedical informatics system (259) called Healthtracker®. This system allows children, parents, and professionals to use a web-based monitoring system to enable more effective treatments, better pathways of shared care, and more equitable and efficient service delivery for children. Healthtracker® is a sophisticated, user-friendly, UK, web-based assessment system launched with Department of Health

support in 2008. It comprises a suite of questionnaires and test games for children and their carers. Importantly, assessments can be accessed via home-based computer for convenience and lower costs. This helps circumvent the many practical difficulties associated with long-term assessment of chronic diseases. Testing is encouraged fun through online computer games, animated characters asking questions, and children can track their own progress.

Outcome choices

The following tools have been selected after thorough review as they best fit the specified inclusion criteria.

Health related Quality of Life (QOL)

- Generic QOL: Paediatric Quality of Life Inventory TM;

Generates physical, psychological, and total score.

o Self report for ages 5-25 years.

o Parent report for ages 2-25 years.

- Disease specific QOL: Multiple Sclerosis Impact Scale-29 version 2 (MSIS-29 v2)

Generates physical, and psychological scores.

o Self report for children 5 years -adulthood

o Parent report.

Fatigue

- Paediatric Quality of Life Inventory[TM]; Multidimensional Fatigue Scale

o Self report for children 5-25 years

o Parent report; for children 2- 25 years

Neuropsychiatric Symptoms

-    Profile Of Neuropsychiatric Symptoms (PONS)

o   Self report for children 5-16 years

o   Parent report

Functioning ; Adaptive behavioural skills

o   Adaptive Behaviour Assessment System II (ABAS II).

-    Parent report for children 5 years –adulthood. Two out of the three domains will be used:

(i)   Conceptual skills: communication, functional academics, and self-direction skills areas

(ii)   Social skills: Social, and leisure skills areas

Cognitive

o   Two Healthtracker online games played by children aged 5-16 years that aim to measure memory, attention and concentration. These are embedded in between questionnaires.

o   Online D2 test game for participants aged 9 years- 60 years. The D2 Test measures processing speed and quality of performance of individuals, allowing for a neuropsychological estimation of individual attention and concentration performance.

CONCLUSIONS

The set up of the Paediatric UK Demyelinating Disease Longitudinal Study (PUDDLS), a prospective multicentre longitudinal observational study, will help to determine the natural history, predictors and outcomes of childhood acquired demyelinating syndromes. I also envisage that that by facilitating the establishment of a biological sample biobank (CSF, serum, and DNA), I will enable future hypothesis driven research. For example, the future discovery of a biomarker will allow validation within this dataset for the evaluation of novel biomarkers. In addition, establishing baseline detailed objective outcome, patient reported and proxy outcome measures will facilitate both primary secondary outcome measurement and power analyses for future clinical trials. The study will also allow our group to collaborate internationally with the International Paediatric Multiple Sclerosis Study Group when future mutual studies are proposed. A paediatric population should reflect the vanguard of MS epidemiological changes and may reflect trends yet to be observed in adult MS cohorts. The restricted window between clinical expression of disease and exposure to environmental factors in children offers a unique research opportunity. Studying a paediatric population from the first demyelinating event will also allow us to investigate the changing epidemiology of MS, and may offer further valuable insights into the genetic and environmental interactions in the pathogenesis of MS.

4.2 Considerations in the design of paediatric MS and ADS clinical trials

Background

New MS drugs are emerging with reported better efficacy in adults than current injectables. European regulation and directives in 2007 have provided a framework with an obligation to perform paediatric studies on any new molecule. New drugs hence require a Paediatric Investigation Plan (PIP) aimed at ensuring that necessary robust data are obtained through studies in children to support authorisation by the European medicines agency (EMA). To date eight new MS drugs have been granted PIP approval by the EMA (Table 52). PIPs initially approved often specify designs as in large adult randomised controlled trials (RCTs). Given there are no RCTs in MS children to date, this situation gives rise to unique but obvious practical and ethical dilemmas.

Most data suggest that paediatric MS largely behaves like adult MS suggesting similar disease processes. For example, similar to adults, children: usually have a clinical relapsing remitting disease course with a clinically isolated syndrome as the first attack; are likely to have been previously infected with the Ebstein Barr virus; and have positive CSF oligoclonal bands (5, 221). However, children probably have a higher MRI lesion load at onset and higher relapse rate than in adult MS, but slower accumulation of disability (11, 260, 261). In addition ADEM is more common in children than adults, and may be the first presentation of multiple sclerosis (76). Disease modifying treatments (DMT) have been used off-label after being approved in adults, thus there is no approved standard of care (166). In addition, in the UK, it often takes a considerable amount of time (up to 6 months) to obtain Primary Care Trust (PCT) funding for the drugs (mainly due to lack of RCT evidence and recommendations), which is not always guaranteed, hence creating inequalities in care.

Table 52: European Medical Agency Paediatric Investigation Plans for disease modifying therapies in paediatric multiple sclerosis

Drug	Decision date	Administration	Paediatric Investigation Plan
Anti-BAFF monoclonal antibody	Nov 2010	Subcutaneous	Multicentre open-label treatment randomised active comparator (Interferon beta-1a) controlled study to evaluate safety, tolerability, pharmacokinetics and efficacy of anti-BAFF monoclonal antibody in children (10-18 years) with remitting relapsing multiple sclerosis.
BAF 312	July 2010	Oral	Open-label, randomised, multicentre, multiple dose, active controlled, parallel-group efficacy and safety study of BAF312 in children from 10 to less than 18 years of age with multiple sclerosis with relapsing remitting course. Follow up: Measures to address long term follow-up of potential safety and efficacy issues in relation to paediatric use.
Fingolimod	Dec 2008	oral	Open label, randomized, multicentre, multiple dose, active controlled (interferon beta-1a), parallel group trial to evaluate pharmacokinetics, safety and efficacy of Fingolimod using blinded MRI assessment in children from 10 to less than 18 years of age followed by a long-term extension.
Laquinimod sodium	Jan 2011	Oral	Randomised, multicentre, parallel group, active controlled trial to evaluate safety, tolerability and effect of oral Laquinimod , compared to disease modifying treatment in children from 10 years to less than 18 years with relapsing remitting multiple sclerosis (RRMS) using blinded MRI assessment. Follow up: Measures to address long term follow-up of potential safety and efficacy issues in relation to paediatric use.
Dimethyl fumarate (BG00012)	Feb 2011	Oral	Open-label, randomised, multicentre, multiple dose, active controlled, parallel-group efficacy and safety study of Dimethyl fumarate in children from 10 to less than 18 years of age with relapsing-remitting multiple sclerosis. Measures to address long term follow-up of potential safety and efficacy issues in relation to paediatric use

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Drug	Decision date	Administration	Paediatric Investigation Plans
Ocrelizumab	May 2011	Intravenous	Randomised open label active-control parallel-group superiority study to evaluate safety and efficacy of ocrelizumab in comparison with active comparator (interferon beta-1a) in children from 10 to less than 18 years old with relapsing remitting multiple sclerosis. Measures to address long term follow-up of potential safety and efficacy issues in relation to paediatric use.
Teriflunomide	July 2011	Oral	Open label, randomized, multicentre, active controlled (interferon beta 1a), parallel group trial to evaluate efficacy, safety/tolerability and pharmacokinetics of Teriflunomide in children and adolescents 10 to less than 18 years of age with multiple sclerosis with relapses using brain MRI assessment followed by a 24 months long-term extension. Follow up: Concerns on potential long term safety and efficacy issues in relation to paediatric use:
Alemtuzumab	Oct 2011	Intravenous	TBA

Challenges for paediatric clinical trials in paediatric ADS and multiple sclerosis:

- There are small numbers of patients available for clinical trials

- Immature immune and nervous system, hence possibly different side effect profiles

- Ongoing growth/ development in children necessitating consideration of different doses

- For younger children, especially those <10 years with regards diagnosis and monitoring:

    – may require sedation for MRI scans

    – the diagnosis of multiple sclerosis may be more challenging

- It is also important to take into consideration the challenges and the expectations of the various parties involved in management of paediatric multiple sclerosis:

    – the community (including families, children, physicians, researchers)

    – regulatory agencies; the requirement by the EMEA for all new drugs to undergo a paediatric investigation plan in order to approve the drugs

    – the pharmaceutical companies, and competing commercial interests (there is an incentive for a 6 month extension of the label).

Expectations for new paediatric dugs:

- Safety: long-term vs short-term: is safety the same in children as adults? Are there effects tolerated in adults that wouldn't be tolerated in children?

    – Example: in October 2004, the US Food and Drug Administration (FDA) directed manufacturers of antidepressants to include a warning stating that antidepressants may increase the risk of suicidal ideation and behaviour in children and adolescents.

- Effectiveness: if drug is effective in adults, how much more evidence is needed in children (given there are no although there are no approved DMT for paediatric MS)?

- Given lack of established evidence, should an active comparator or placebo be used.

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- Dose finding studies in new drugs, due to BMI and metabolism differences, and the need to find the lowest safest dose.

If one takes the view that there is no RCT standard treatment to compare to, one will never reliably (by Randomised Controlled Trial) define the standard treatment. According to regulatory agencies, given that active comparators do not have a good evidence base (only case series conducted), then superiority to comparator or placebo will be necessary using a clinically meaningful surrogate.

One option with regards using new drug therapies in children which were only tested in adults is to use registries as they:

- are easier to enrol to, and include patients requiring treatments, and potentially more 'mildly' affected cases;

- allow complete medical, parental and patient choice as opposed to limiting to the specific clinical trial protocol

- have the potential to estimate health economic costs with longer term follow up

- may supply important information on the natural course of disease and may help in the long term assessment of effectiveness vs safety as the natural course of the disease is not very well known.

Registries hence can help establish 'best standard care' and include patients who choose not to be treated.

Historical controls and registries, however, have well known problems as they:

- cannot eradicate biases due to other factors, aside from treatment, that may have changed over time;

- are unable to control for confounding of selection biases, treatments

- there are often dropouts

An unbiased point estimate of treatment effect, even with wide uncertainty, is preferable to a point estimate with unquantifiable bias. There is potentially a window for clinical trial recruitment when identifying children at first attack who fulfil the new McDonald MS criteria at disease onset for treatment (see chapter 2.5), and are awaiting a relapse before a decision regarding treatment.

Controlled studies with low statistical power in case of an important treatment effect may indeed be preferable to no controlled studies. The following key points need to be considered:

- Ideally a 'hard' and clinically relevant endpoint is used.

- Ideally, I wish to obtain an unbiased estimate of the effect of the treatment being investigated compared to placebo or to another active compound and, for this reason, every effort should be made to randomise patients.

- Where a placebo control may not be possible, an appropriate control group may be 'best standard of care'.

- As current active comparators do not have their own good evidence base (beta interferons), superiority to that comparator will be necessary.

Using adult trial data to inform decisions about clinical trials in children

I might want to use adult trials to (262):

- decide on sample sizes for paediatric trials

- interpret the results of paediatric trials

- estimate how close the results on the same outcomes from adult and paediatric trials might be

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A Bayesian approach can be used (posterior probability = Likelihood x prior Probability). This is because paediatricians often believe drugs effective in adults will be effective in children. Bayesian approaches allow exploiting prior information for sample size calculation, which could minimise unnecessary paediatric experimentations. Small Trials, adaptive designs, futility trials all require: more up front planning; strong evidence to base decisions; and a willingness to stick with exact rules (Table 53).

Table 53: Possible issues which may arise from small, early stopping or adaptive trials

Problem	Reason
Lack of credibility	Small trials are not convincing
Lack of realism	Dramatic treatment difference is implausible
Imprecision	Wide confidence interval for treatment effect
Bias	Trial is liable to stop on a random high or low
Speed	Time spent and information yielded may be insufficient to allow consideration of overall balance of costs and benefits Stopping early can seem more important than completed trial
Pressure	Unduly enthusiastic recommendation for practice may follow
Mistakes	Risk exists for false-positive or false negative results

CLINICAL TRIAL DESIGNS- PRACTICAL EXAMPLES FOR FUTURE TRIALS

(1) Using large phase adult 3 clinical trials to inform paediatric clinical trial design.

In this section I aim to explore potential clinical trial designs, and calculate sample sizes for new MS oral drugs in children.

Methods:

In order to inform clinical trial design requirements for paediatric trials (including sample size) I conducted a secondary analysis of two relapsing-remitting adult MS Fingolimod trials: FREEDOMS (263), a 24-month, double-blind, randomised, placebo controlled- study, (n=1033); and TRANSFORMS (264), a 12-month, double-blind randomised active controlled study, (n=1153). Cochrane's RevMan v5.1 and NQuery sample size software were used for the metanalysis and sample size estimations.

Results:

To conduct an active RCT as in TRANSFORMS and assuming a similar risk ratio (0.62) for relapse in the study period and a similar event number, a sample size (equal numbers in both arms) of 436 children is required (power 80% and alpha 5%). Sample size for a placebo RCT with same assumptions is n=134. If the event rate is higher in children than in adults (eg. by 50%) the required sample size for an active RCT is n=248. Assuming that MS is the same in adults as in children so that adult data is considered replicable in children but additional paediatric data is collected to perform a planned metanalysis of the TRANSFORMS + FREEDOMS + paediatric RCT, the calculated sample size is n=183 (121 experimental arm; 62 active arm). Appendix 0 details the metaanalysis, sample size calculations, and assumptions

used when extrapolating from the FREEDOMS and TRANSFORMS trials for the relapse rates and MRI outcome measures.

Secondary outcomes (MRI findings and functional disability) are problematic in children, as cognitive function, schooling and quality of life need to be considered.

(2) Using published paediatric relapse rates to calculate samples sizes for a clinical trial

Published paediatric relapse rates (Table 9) make sample size calculations possible as relapse rates are accepted as the primary outcome measure in multiple sclerosis clinical trials. The negative binomial model is increasingly used to calculate sample sizes in multiple sclerosis clinical trials (265) due to the wide variability present in individual relapse rates. Assuming a baseline relapse rate of 0.85/year and a new drug with 50% efficacy, a total sample size of n=804 would be required (power 80% alpha 0.05). Appendix 6 shows the sample size calculations for different relapse rates and power assumptions.

(3) Designing a transverse myelitis treatment trial

Background; the unmet clinical need and need for trials

Transverse myelitis (TM) is a rare (incidence 3-7/million/year) immune-mediated disorder of the spinal cord affecting children and adults. In TM, spinal cord dysfunction presents acutely/subacutely with motor (weakness of the limbs), sensory, and sphincter disturbance which may be asymmetric with varied presentation and severity (50). MRI lesions do not always result in a corresponding clinical sensory level (45). Despite there being no biomarker available, TM is usually accompanied by changes in neuroimaging and a reactive cerebro-spinal fluid analysis, which complements the clinical presentation in making a diagnosis of TM, as emphasised by the TM Consortium Working Group diagnostic criteria (Chapter 1.4).

Most children reach a nadir within the first 1-2 weeks of presentation. A 'plateau' phase typically lasts for approximately one week before ongoing recovery begins. The initial recovery period may extend to several months after the initial insult. The widely accepted American Spinal Injury Association (ASIA) scale of myelopathy, rates patients according to severity:

A = Complete: No motor or sensory function is preserved in the sacral segments S4-S5

B = Incomplete: Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.

C = Incomplete: Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.

D = Incomplete: Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.

E = Normal: Motor and sensory function are normal.

The disease leads to varying levels of permanent disability in a majority of children and adults. Early recognition, diagnosis and treatment are considered vital to the management of this condition. Despite this, there currently remain no robust controlled trials for the treatment of TM, in children or adults, to inform on the optimal early treatment of TM. The current management recommendation is largely based on an evidence-based review commissioned by the American Academy of Neurology (266). Children and adults are now treated with high dose intravenous steroids for 3-7 days to reduce inflammation based on Class IV evidence. Plasma exchange (PLEX) is increasingly used in children and adults with acute fulminant central nervous system (CNS) demyelination including TM. The efficacy of PLEX was demonstrated in a small randomized controlled trial in adults with acute central

nervous system (CNS) demyelination (including 4 patients with TM) where steroids had failed to induce a remission of symptoms (160). Another promising potential early treatment for patients with TM is intravenous immunoglobulins (IVIg). In children who do not respond to steroids, intravenous immunoglobulin is often used, although supporting data are limited to small case series and single case reports (5, 42). IVIg is used increasingly in the management of a range of neurological conditions, and its efficacy has been established clearly in randomised controlled trials for some such as Guillain-Barre syndrome and chronic inflammatory demyelinating polyradiculoneuropathy (267). The relevant immune-pathological mechanisms attenuated by IVIg in other neurological disease are likely to be present in TM (268), providing a strong rationale for its use in the management of acute TM.

There is hence a need to design therapies for this devastating condition in order to ameliorate disability. In the next section I will consider considerations regarding sample size calculations in this rare disorder to conduct a trial to establish whether early treatment with IVIg is of extra benefit in acute TM when compared to intravenous steroids, the current standard therapy.

Considerations for study design, particularly sample size, for hypothetical TM trial

The following treatment arms to be considered:

- Arm 1: Control arm, high dose intravenous methylprednisolone (IVMP)

- Arm 2: Intervention arm, high dose methylprednisolone with IV Immunoglobulin (IVIG).

The proposed outcome measure will be the proportion of a 2 point improvement on the ASIA scale (classified A – E). The proposed inclusion criteria will be patients presenting with TM and an ASIA severity scale of A-C.

The assumptions of the sample size calculation have been based on the conclusions of pilot data from a one centre retrospective cohort study (Birmingham Children's Hospital). Twenty four patients were followed over a 6 month period; their progress was measured by classification on the ASIA scale. Patients were given a range of treatments including (IVMP, IVIG, intravenous cyclophosphamide, and plasmapharesis). The results of patents that were classified as C or above (n=19), in line with the inclusion criteria for the proposed RCT are shown in Table 54. This table demonstrates certain points I used in my decision surrounding the power calculation: 1) no patients showed any deterioration on the scale; 2) 50% of patients improved by 2 points or more. Thus I assumed that the proportion of participants showing a 2 point improvement (or greater) on the ASIA classification will be approximately 0.5 (50%) in the control arm and a minimum of 0.75 (75%) in the intervention arm. I propose that the minimum clinically important difference in percentages between the intervention / control group will be 25% observable at 24 weeks post randomisation. I believe these estimates are realistic based on the existing data and given the measures in place to maintain retention in the trial. Attrition will be accounted for in the sample size, at estimated value of 10%.

Table 54: ASIA scale at onset and at 6 month follow up for n=19 children followed up at Birmingham Children's Hospital

Starting Classification	N=19	0 point improvement	1 point improvement	2 point improvement	3 point improvement
A	8	1	3	2	2
B	2	0	1	0	1
C	9	0	5	4	-

Sample size and power analyses

An overall sample size of 188 participants, 94 in each group, (randomised 1:1 to control arm: intervention arm) would provide 90% power to detect a 25% difference in the proportion of 2 point improvement or greater on the ASIA scale for the control verses intervention comparisons. Appendix 6 provides details for the analysis plan.

The main barrier to conducting this proposed trial is the sample size of 188. According to the national surveillance study I conducted, one expects n=26 children per year presenting with TM (Chapter 2.3). A potential solution would be to conduct a multicentre trial which includes both children and adults. This scenario is feasible as TM affects adults and children with a similar presentation, severity and primary outcomes. This means that clinical trial results could be applied across all ages, with post hoc subgroup and sensitivity analyses providing further information.

CONCLUSIONS

MS adult trial designs cannot be used as a template for paediatric studies as: effects and the balance of benefit and harm may differ; outcome measures used in adults are problematic; small populations present challenges. In this section I presented possible solutions including methodologies that borrow strength from adult studies; using primary outcome measures that are applicable across the ages to include children in future trials. Secondary outcome measures which are child specific and core outcome measures for this patient group will need to be refined and agreed internationally.

CHAPTER 5 THESIS CONCLUSIONS

I report the highest surveillance incidence rates (approximately 1 per 100,000 children/ year) of childhood acquired demyelinating syndromes ADS to date and show that children of non-white ethnicity are not underrepresented as expected from adult MS studies. I discuss several clinical features for example, that clinically isolated syndrome (CIS) presentations are twice more common than acute disseminated encephalomyelitis (ADEM); and that optic neuritis is more commonly unilateral than bilateral. This work also shows that in childhood ADS, sex ratios varied with age, with more females in older age groups. The observations regarding the demographics of childhood ADS support the hypothesis that changing environmental risk factors for MS may indeed be operating in childhood, hence having implications for future preventative studies (such as use of Vitamin D supplementation). This is also the first study which has applied the newly revised MS 2010 Macdonald diagnostic criteria in a prospective population based series. I showed that a minimum 24% of first onset met criteria for being at high risk of MS diagnosis at first ADS presentation and hence were potentially eligible for early disease modifying treatment. The variable treatments given at first acute ADS presentation also highlights the need for future clinical trials for acute ADS therapies.

The potential to diagnose MS at disease onset has implications for MRI protocols for children with suspected ADS, and individual patient treatment decisions. To date, eight new MS drugs have been recommended for a Paediatric Investigation Plan, hence earlier diagnosis may increase the eligible clinical trial population.

In a one year follow up of the national surveillance study, I confirm that children presenting with a CIS are more likely to have a clinical relapse than those with ADEM over the course of

one year. This has important implications with regards monitoring and the requirement of repeating an MRI scan after an interval. Currently with the wide availability of MRI, an increasing number of children are having follow up scans. I have highlighted the wide differential diagnoses in a prospective national study, which supports the need for standardised guidelines, protocols, and education programmes. This is an important factor to consider when drawing up guidelines for childhood multiple sclerosis, and relapsing inflammatory demyelinating diseases. I showed that children with ADEM have several MRI features on initial presentation that additionally appear to distinguish them from polyfocal CIS. The new McDonald 2010 MS criteria appear to have good overall specificity and sensitivity (over 80%) for children presenting with CIS. However, on univariate analysis there were other factors (besides MRI) that were important to take into account when predicting outcome such as age; and particularly CSF oligoclonal bands. Previous international studies (this is the first study of its kind in the UK) have tended to focus on clinical features, MRI features and CSF oligoclonal bands in isolation. By combining these factors in a clinical algorithm, I have shown that more useful models could be devised. These findings need to be validated in collaboration with other groups internationally.

In this thesis work I also describe a series of longitudinal retrospective case series delineating prognostic risk factors. In a retrospective analysis of 38 childhood onset MS cases from three UK demyelination clinics was conducted, I showed that at first MRI scan, the 2010 McDonald MRI criteria hence appeared more sensitive than the recommended 2007 IPMSSG and may allow MS diagnosis at first presentation of CIS in at least a half of cases. In another multicentre longitudinal retrospective case series including 44 children I show that childhood optic neuritis is associated with severe visual deficit with good recovery. An initial abnormal MRI brain scan or relapsing optic neuritis should were strong predictors for to MS or NMO

diagnosis. In another population based study involving intensive care units I show that ADEM is potentially a severe disorder and may result in death. In another study I described a historical neuromyelitis optica (NMO) longitudinal cohort (n=22) with known aquaporin-4 antibody (AQP4-ab) status and compare it to a contemporary incident national cohort sample. As in other adult and paediatric series, NMO predominantly affects females. This cohort confirms that brain involvement is common in paediatric NMO with nearly two thirds having an abnormal MRI brain scan compared with adult NMO (25%). It is important to recognise the spectrum of brain abnormalities in NMO as the occurrence of such lesions and sometimes the presence of encephalopathy and polyfocal neurological deficits may resemble ADEM, with misleading implications as to prognosis and therapy. In addition I showed thatAQP4-Ab positivity is associated with early recurrence and visual disability.

The set up of the Paediatric UK Demyelinating Disease Longitudinal Study (PUDDLS), a prospective multicentre longitudinal observational study, will help to determine the natural history, predictors and outcomes of childhood acquired demyelinating syndromes. I also envisage that that by facilitating the establishment of a biological sample biobank (CSF, serum, and DNA), I will enable future hypothesis driven research. For example, the future discovery of a biomarker will allow validation within this dataset for the evaluation of novel biomarkers. In addition, establishing baseline detailed objective outcome, patient reported and proxy outcome measures will facilitate both primary secondary outcome measurement and power analyses for future clinical trials. The restricted window between clinical expression of disease and exposure to environmental factors in children offers a unique research opportunity. Longitudinally studying a paediatric population from the first demyelinating event will also allow us to investigate the changing epidemiology of MS, and

may offer further valuable insights into the genetic and environmental interactions in the pathogenesis of MS.

I described key concepts important for the design of the first future clinical trials and preventative studies in ADS and MS. The potential to diagnose MS at disease onset has implications for MRI protocols for children with suspected ADS, and individual patient treatment decisions. This observation may be particularly important as new MS drugs are emerging with reported better efficacy in adults than current injectables, and the simultaneous requirement for new drugs to undergo testing in children with the aim of ensuring robust evidence to support authorisation by the European Medicines Agency. To date, eight new MS drugs have been recommended for a Paediatric Investigation Plan, hence earlier diagnosis may increase the eligible clinical trial population. Allowing children to enter these studies at an earlier stage might optimise outcomes but also would involve attendant burdens and potential risk. I presented possible solutions including methodologies that borrow strength from adult studies; using primary outcome measures that are applicable across the ages to include children in future trials. Secondary outcome measures which are child specific and core outcome measures for this patient group will need to be refined and agreed internationally. MS adult trial designs cannot be used as a template for paediatric studies as: effects and the balance of benefit and harm may differ; outcome measures used in adults are problematic; small populations present challenges.

The detailed study of ADS presented in this work I hope will help to inform future clinical service delivery and clinical trial design.

APPENDICES

1. Surveillance Case Notification Questionnaire

UK and Ireland Childhood Inflammatory Demyelinating Disease Surveillance Study (UCID-SS)
BPSU facilitated Data Collection Proforma

BPSU case ref._____

REPORTING Instructions: Please report children (younger than 16 years) experiencing clinical neurological events consistent with site specific inflammatory CNS demyelination and confirmed with **white matter changes on MRI** (except in optic neuritis) as in table on page 2. Please only report children presenting with their **first** demyelinating episode.

Details of clinician completing form:
Name: _____
Hospital name: _____
Telephone number: _____
E-mail: _____
Date completed:___ /___ /___

SECTION 1 – PATIENT INFORMATION for anonymised linkage

Date of birth (dd/mm/yyyy):   ____ /_____ /_____

Sex: Male ☐   Female ☐

NHS number: _____

Has the patient been referred to you from another hospital? ☐ Yes ☐ No

If Yes, please give: Name of referring Consultant: _____ Hospital:_____

Home Post Code (First half only): ☐☐☐

Ethnic Origin:

☐ White

Asian or Asian British:
☐ Indian
☐ Pakistani
☐ Bangladeshi
☐ Chinese

☐ Mixed; please specify_____

Black or Black British:
☐ Caribbean
☐ African
☐ Any other Black Background
☐ Other Ethnic group; please specify_____

Was the patient born in the UK? Yes ☐ No ☐ if no: specify country of birth: _____

REPORTING INSTRUCTIONS (please tick):

Condition	Reporting Definition
Acute Disseminated encephalomyelitis (ADEM) ☐	Any case with: (i) Clinical event (subacute/acute, poly-symptomatic **and includes encephalopathy**) due to a presumed inflammatory or demyelinating cause affecting multifocal areas of the CNS. (ii) MRI white matter changes.
Clinically Isolated Episode (CIS) ☐	Any case with a first acute clinical episode of CNS inflammatory demyelination (monofocal or multifocal but **does not include encephalopathy**) with white matter changes on the MRI.
Transverse Myelitis ☐	Any case with weakness and/or numbness of both legs (with or without involvement of arms) and supported by demyelination on MRI spine.
☐ Optic Neuritis	Any case of subacute/acute loss of vision with a presumed demyelinating origin.
Neuro-myelitis optica ☐ (NMO)	Please report any case of optic neuritis and associated myelitis.

SECTION 2 – CLINICAL FEATURES

2.1 Onset of demyelinating event (dd/mm/yyyy): _____ /_____ /_____

2.2 Date of admission:_____/_____/_____

2.3 Did the child die before discharge? ☐No   ☐Yes: Date of death: _____/_____/_____

Cause of death on death certificate or from post-mortem results: _____

_____

2.4 Demyelinating signs and symptoms (Mark all that apply)

☐ Bilateral visual loss (involvement of both eyes within 30 days of each other)	☐ Loss of balance (gait ataxia)
☐ Unilateral visual loss (one eye only)	☐ Impaired co-ordination of arms/legs (limb ataxia)
☐ Double vision	☐ Confusion or impaired alertness (encephalopathy)
☐ Intranuclear ophthalmoplegia	☐ Fever
☐ Facial pain and numbness	☐ Neck Stiffness
☐ Loss of sensation (one side of face only without facial pain)	☐ Headache
☐ Other cranial nerve signs:_____	☐ Seizures
☐ Weakness (one side of face only)	☐ Dizziness +/– nausea
☐ Loss of sensation (one sided, involving face, arm and leg)	☐ Fatigue
☐ Weakness (arm and leg +/– face, all on same side of body)	☐ L'Hermitte's symptom (electrical sensation down the back produced by bending the neck forward).
☐ Loss of sensation (both legs and/or both arms at the same time)	☐ Other (please specify): _____
☐ Weakness (both legs and/or both arms)	_____
☐ Bladder retention +/– bowel dysfunction	

2.5 Was an MRI performed?: ☐Yes but CT was performed first ☐Yes   ☐No   ☐Unknown

If Yes: ☐ Brain with contrast ☐ Brain without contrast ☐ Brain – unknown if contrast used   ☐ Spine

2.6 If performed, was the MRI abnormal?: ☐Yes   ☐No   ☐Unknown

Please give date and details:_____

2.7 CSF:- positive for oligoclonal bands: ☐Yes   ☐No   ☐Unknown   ☐ Not done

2.8 CSF details:- WCC_____x10^6/L   RBC_____x10^6/L   protein_____g/L

Please return all 3 pages in the prepaid envelope to Dr Michael Absoud, Fourth Floor, Institute of Child Health, Birmingham Children's Hospital, Steelhouse Lane, Birmingham B4 6NH   2/3

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2.9 Other relevant investigations:

VEPs/ERG	☐Unknown	☐No	☐Yes _____
EEG	☐Unknown	☐No	☐Yes _____
NMO Antibody	☐Unknown	☐No	☐Yes _____
Other	☐Unknown	☐No	☐Yes _____

Microbiology infectious agent identified   _____

2.10 Did the child require treatment? ☐Yes   ☐No

Treatment	Tick if applies	Details (drug name, dosage, number of days)
IV Methylprednisolone		
Oral prednisolone		
Intravenous Immunoglobulin		
Antimicrobials used (eg antibiotics/antivirals)		
Anti-epileptics used		
Intensive care stay		

2.11 Was the possibility of future recurrent demyelination (i.e. multiple sclerosis) discussed with the family?

☐Yes   ☐No   ☐Unknown

SECTION 3 – RELEVANT MEDICAL AND FAMILY HISTORY

3.1 Is there a known patient history of (*important for consideration of the differential diagnosis*):

- Autoimmune Disorder (eg. diabetes, thyroid disease, JIA, SLE):

☐Yes _____   ☐No   ☐Unknown

- Other medical history:

☐Yes _____   ☐No   ☐Unknown

- Does the patient have prior developmental delay, known neurological condition, visual impairment or learning difficulties: ☐Yes   ☐No   ☐Unknown

If Yes, please specify; _____

3.2 Is there a family history of:

Multiple sclerosis: ☐Yes   ☐No   ☐Unknown;   Relationship to patient: _____

Autoimmune Disorder: ☐Yes _____   ☐No   ☐Unknown;   Relationship to patient _____

Thank you for your time and help in completing this questionnaire.

2. Surveillance Outcome Questionnaire

UK and Ireland Childhood Inflammatory Demyelinating Disease Surveillance Study
(UCID-SS)
BPSU facilitated Data Collection Follow-up Proforma

☐Year 1   ☐Year 2

Reporting Information	
BPSU case ref:	
Follow Up Date:	
Date Today:	
Case Definition (see protocol):	

Details of clinician completing form:

Name: _____

Hospital name: _____

Telephone number: _____

E-mail: _____

Date completed:___/___/___

SECTION 1 – PATIENT INFORMATION for anonymised linkage

Date of birth (dd/mm/yyyy):   ____ /_____ /_____

Sex: Male ☐   Female ☐

NHS number: _____

Is the child is still under your care? ☐ Yes ☐ No   ☐ Discharged

If No to whom has the child been referred to:

Consultant name: _____ Hospital name:_____

SECTION 2 – FURTHER EPISODES OF DEMYELINATION

2.1 Any further episodes of demyelination over the past 12 months?   Yes ☐ No ☐   How many? _____

(If No- go to section 3)

2.2 Nature of episodes: please complete one page for each subsequent episode.

DATE of episode *(dd-mm-yyyy)*: _____/_____/_____	
SIGNS AND SYMPTOMS: ☐ Bilateral visual loss (involvement of both eyes within 30 days of each other) ☐ Unilateral visual loss (one eye only) ☐ Double vision ☐ Intranuclear Ophthalmoplegia ☐ Facial pain and numbness ☐ Loss of sensation (one side of face only without facial pain) ☐ Other Cranial Nerve signs: _____ ☐ Weakness (one side of face only) ☐ Loss of sensation (one sided, involving face, arm and leg) ☐ Weakness (arm and leg +/– face, all on same side of body) ☐ Loss of sensation (both legs and/or both arms at the same time)	☐ Weakness (both legs and/or both arms) ☐ Bladder retention +/– bowel dysfunction ☐ Loss of balance (gait ataxia) ☐ Impaired co-ordination of arms/legs (limb ataxia) ☐ Confusion or impaired alertness (encephalopathy) ☐ Fever ☐ Neck Stiffness ☐ Headache ☐ Seizures ☐ Dizziness +/– nausea ☐ Fatigue ☐ L'Hermitte's symptom (electrical sensation down the back produced by bending the neck forward). ☐ Other (please specify): _____ _____
Brain MRI	Date (*dd-mm-yyyy)*: _____ White matter lesions (Y/N):_____ ❑ Not done/ Information not available
Spinal MRI	Date (*dd-mm-yyyy)*: _____ White matter lesions (Y/N):_____ ❑ Not done/ Information not available
CSF Oligoclonal Bands	❑ Positive ❑ Negative ❑ Not done ❑ Unknown **or** Not asked
Acute treatment used	Medications: Duration: Side effects:
Diagnosis given	❑ MS ❑ ADEM ❑ CIS ❑ Transverse myelitis ❑ Optic neuritis ❑ NMO ❑ Other; specify:
Did the child die?	No ☐ Yes ☐ Date: _____/_____/_____ Cause of death:_____

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DATE of episode *(dd-mm-yyyy)*: ____/_____/_____	

SIGNS AND SYMPTOMS: ☐ Bilateral visual loss (involvement of both eyes within 30 days of each other) ☐ Unilateral visual loss (one eye only) ☐ Double vision ☐ Intranuclear Ophthalmoplegia ☐ Facial pain and numbness ☐ Loss of sensation (one side of face only without facial pain) ☐ Other Cranial Nerve signs: _____ ☐ Weakness (one side of face only) ☐ Loss of sensation (one sided, involving face, arm and leg) ☐ Weakness (arm and leg +/– face, all on same side of body) ☐ Loss of sensation (both legs and/or both arms at the same time)	☐ Weakness (both legs and/or both arms) ☐ Bladder retention +/– bowel dysfunction ☐ Loss of balance (gait ataxia) ☐ Impaired co-ordination of arms/legs (limb ataxia) ☐ Confusion or impaired alertness (encephalopathy) ☐ Fever ☐ Neck Stiffness ☐ Headache ☐ Seizures ☐ Dizziness +/– nausea ☐ Fatigue ☐ L'Hermitte's symptom (electrical sensation down the back produced by bending the neck forward). ☐ Other (please specify): _____ _____
Brain MRI	Date (*dd-mm-yyyy)*: _____ White matter lesions (Y/N):_____ ❏ Not done/ Information not available
Spinal MRI	Date (*dd-mm-yyyy)*: _____ White matter lesions (Y/N):_____ ❏ Not done/ Information not available
CSF Oligoclonal Bands	❏ Positive ❏ Negative ❏ Not done ❏ Unknown **or** Not asked
Acute treatment used	Medications: Duration: Side effects:
Diagnosis given	❏ MS ❏ ADEM ❏ CIS ❏ Transverse myelitis ❏ Optic neuritis ❏ NMO ❏ Other; specify:
Did the child die?	No ☐ Yes ☐ Date: _____/_____/_____ Cause of death:_____

Please photocopy page and complete if further episodes have occurred

SECTION 3. CURRENT FUNCTIONAL STATUS

- When was the Date of last clinic visit? _____/_____/_____

MOBILITY/ MOTOR:

a. Does the patient have a motor impairment or limitations on mobility?

   No ☐   Yes☐   (If yes tick one box in each section)   ☐Unknown

☐ Limits participation because of gait, no aids required ☐ Uses aid occasionally ☐ Uses aid for majority of time ☐ Wheelchair –also walks for short distances ☐ Wheelchair-dependent	the primary cause of limited mobility is: ☐ Ataxia ☐ Hemiparesis ☐ Quadriplegia ☐ Diplegia

b. Were there any difficulties with fine motor skills? _____

c. Did the child have upper limb ataxia? _____

d. Does the child receive therapy (such as physiotherapy, occupational, speech therapy?)

☐Unknown   ☐No   ☐Yes (please specify)_____

VISION:

Visual acuity: right eye __/__   left eye __/__   (best corrected acuity)   ☐Unknown

☐ Normal vision (visual acuity 6/9 or better) ☐ Decreased vision, but not registered visually impaired (6/12 or better) ☐ Registered with partial visual impairment (6/60 or better) ☐ Registered severely visually impaired (worse than 6/60)

COGNITIVE:

☐ No concerns ☐ Above average/ Normal (functions well in school) ☐ Minimal difficulties (on special education needs register, or School action support) ☐ Moderate difficulties (statement of education) ☐ Severe difficulties (Special School) ☐ Unknown or not asked

BOWEL/BLADDER:

☐ Normal age-related bedwetting/soiling ☐ Minimal (urinary hesitancy/urgency but no bed wetting/soiling) ☐ Moderate (loses bladder/bowel control rarely <1x/wk) ☐ Severe (loses bladder/bowel control >1x/wk) ☐ Unknown or Not asked

Other SELECTED SYMPTOMS and SIGNS   (Please add comments below):

Has the patient suffered from Fatigue affecting activities of daily living?	☐ Yes	☐ No	☐ Not asked	
Has the patient suffered from focal symptomatic Seizures?	☐ Yes	☐ No	☐ Not asked	
Has the patient suffered from symptoms of depression requiring further psychological input?	☐ Yes	☐ No	☐ Not asked	

Thank you for your time and help in completing this questionnaire.

4. Paediatric UK demyelinating disease longitudinal study (PUDDLS) PROTOCOL

BMC
Pediatrics

STUDY PROTOCOL | **Open Access**

Paediatric UK demyelinating disease longitudinal study (PUDDLS)

Michael Absoud[1,2*], Carole Cummins[1], Wui K Chong[3], Christian De Goede[4], Katharine Foster[5], Roxanna Gunny[3], Cheryl Hemingway[6], Philip Jardine[7], Rachel Kneen[8], Marcus Likeman[9], Ming J Lim[10], Mike Pike[11], Naomi Sibtain[12], William P Whitehouse[13] and Evangeline Wassmer[2]

ABSTRACT

Background: There is evidence that at least 5% of Multiple sclerosis (MS) cases manifest in childhood. Children with MS present with a demyelinating episode involving single or multiple symptoms prior to developing a second event (usually within two years) to then meet criteria for diagnosis. There is evidence from adult cohorts that the incidence and sex ratios of MS are changing and that children of immigrants have a higher risk for developing MS. A paediatric population should reflect the vanguard of such changes and may reflect trends yet to be observed in adult cohorts. Studying a paediatric population from the first demyelinating event will allow us to test these hypotheses, and may offer further valuable insights into the genetic and environmental interactions in the pathogenesis of MS.

Methods/Design: The Paediatric UK Demyelinating Disease Longitudinal Study (PUDDLS) is a prospective longitudinal observational study which aims to determine the natural history, predictors and outcomes of childhood CNS inflammatory demyelinating diseases. PUDDLS will involve centres in the UK, and will establish a cohort of children affected with a first CNS inflammatory demyelinating event for long-term follow up by recruiting for approximately 5 years. PUDDLS will also establish a biological sample archive (CSF, serum, and DNA), allowing future hypothesis driven research. For example, the future discovery of a biomarker will allow validation within this dataset for the evaluation of novel biomarkers. Patients will also be requested to consent to be contacted in the future. A secondary aim is to collaborate internationally with the International Paediatric Multiple Sclerosis Study Group when future collaborative studies are proposed, whilst sharing a minimal anonymised dataset. PUDDLS is the second of two jointly funded studies. The first (UCID-SS) is an epidemiological surveillance study that already received ethical approvals, and started on the 1st September 2009. There is no direct patient involvement, and UCID-SS aims to determine the UK and Ireland incidence of CNS inflammatory demyelinating disorders in children under 16 years.

Discussion: A paediatric population should reflect the vanguard of MS epidemiological changes and may reflect trends yet to be observed in adult MS cohorts. The restricted window between clinical expression of disease and exposure to environmental factors in children offers a unique research opportunity. Studying a paediatric population from the first demyelinating event will allow us to investigate the changing epidemiology of MS, and may

offer further valuable insights into the genetic and environmental interactions in the pathogenesis of MS.

BACKGROUND

Introduction
CNS inflammatory demyelinating diseases (CIDD) are rare childhood disorders but may culminate in physical and cognitive disability or ultimately be diagnosed as Multiple Sclerosis (MS). MS is a chronic inflammatory demyelinating disease of the CNS characterized by myelin loss, axonal degeneration and, often, progressive neurological dysfunction, that is usually relapsing remitting at onset. The incidence of childhood CIDD is unknown, and the UK and Ireland Childhood Inflammatory Demyelination Surveillance Study (UCID-SS) is already underway to determine this. At the first presentation of a CNS inflammatory demyelinating event, children are diagnosed with either an acute disseminated encephalomyelitis (ADEM), optic neuritis, transverse myelitis, or another clinically isolated episode (CIS). Children who present with a CNS inflammatory demyelinating episode involving single or multiple symptoms may later present with a second event (majority usually within two years) to then meet criteria for MS diagnosis(6). There is evidence that at least 5% of MS cases manifest in childhood(269). It is not clear at the first onset of symptoms which children will go on to develop MS.

Prospective studies are required
The available literature on paediatric MS, is primarily limited to smaller case series and larger retrospective reviews of established adult MS populations(11, 26, 31, 39, 77, 83, 176, 221, 251-256). The International Paediatric MS Study Group, (www.ipmssg.org) have recently published consensus definitions of paediatric CNS inflammatory demyelinating disorders and MS to help facilitate uniformity in future research(12). Evidence for differences in natural history of childhood onset MS(5) are also primarily derived from retrospective cohorts, as are studies linking environmental factors (EBV infections or Vitamin D deficiency) with possible MS development(257). The risk of relapse in children and hence the risk of developing MS may be geographically different(6). There is hence an urgent need for prospective population based studies to further understand clinical, radiological, and pathobiological features as well as outcome of childhood onset inflammatory demyelinating disease.

Paediatric cohort may reveal new trends
Various new trends in adult MS have been reported (reviewed in ref (2)), which include geographic rising rate of MS, and a rising female to male sex ratio by year of birth (3). There is evidence that Indian and Pakistani immigrants who entered England younger than 15 had a higher risk of developing MS than those that entered after this age(1). The vanguard of any change in trends in the epidemiology of MS is likely to be evident in a paediatric population. Genetic epidemiology to date supports the dual role of "nature and nurture" in MS pathobiology(2). As such paediatric cohorts can also offer further valuable insights into the genetic and environmental interactions in the pathogenesis of MS. The corner stone of cohorts that are likely to be able to address complex disorders such as MS, depend on the availability of biological sample with comprehensive databases with clinical information.

New criteria for diagnosis for paediatric MS require evaluation
At first presentation of CIDD, children are diagnosed with optic neuritis, transverse myelitis, other clinically isolated episodes (CIS) or acute disseminated encephalomyelitis (ADEM). The

newly proposed consensus definitions(12) for CIDD are operational and require evaluation in prospectively followed up cohorts. For isolated monophasic syndromes, normal MRI and cerebrospinal fluid (CSF) are thought to predict a very low risk for development of MS in adults (86). However the same may not be true for children. In addition the differential diagnosis for childhood demyelinating disease and MS (documented in exclusion criteria) is much wider than that in adults. Furthermore, MRI criteria used in adults to diagnose MS e.g. MRI McDonald criteria may not be valid in children (24, 91, 224). The utilisation of revised McDonald criteria(67) and others including the KIDMUS MRI criteria (77) for paediatric MS need to be validated in new cohorts.

McDonald et al. (67) criteria:
Three of: 1) ≥9 white matter lesions or 1 gadolinium enhancing lesion, 2) ≥3 periventricular lesions, 3) 1 juxtacortical lesion, 4) an infratentorial lesion.

KIDMUS (77) criteria:
All of: ≥1 lesion perpendicular to long axis of corpus callosum; sole presence of well defined lesions

No available biomarker for MS
In line with adult based studies (258), there is no currently available biomarker that fulfils the criteria of a surrogate endpoint in MS in children. Current routine tests including CSF oligoclonal bands, lack sensitivity and specificity in individuals presenting with a first CNS inflammatory demyelinating event. A precondition for the identification of biomarkers is a well described and prospectively followed clinical cohort and the availability of stored tissue linked to relevant clinical information.

Early diagnosis allows for early treatment
For relapses or attacks of MS, corticosteroids are the mainstay of treatment. Early initiation of "disease modifying agents", such as beta interferon and glatiramer acetate appears to be of benefit in adults. Thus, it is more critical than ever to accurately diagnose MS as early as possible. However, very little is published on the use of interferon in children (161-165). The determination of the longitudinal outcome of the first CNS inflammatory demyelinating episode in children is an essential pre-requisite for the design of any prevention or treatment trials. Prediction of outcome at an early stage is critical to quantify the risk to benefit ratio of any intervention.

The need to know the extent of disease burden
Furthermore, identifying the natural history and outcomes of paediatric MS in the UK has major implications when planning service provisions, where there is evolving evidence of lack of awareness, and patchy service provision. At the Paediatric MS meeting, London November 2007 (attended by families and multidisciplinary professionals) there was a call for a better understanding of long-term outcomes including quality of life, cognitive, adaptive behavioural and functional skills, neuropsychiatric symptoms, and treatment effects for children presenting with CNS inflammatory demyelination.

Context of study in relation to current practice

Children with CNS inflammatory demyelination are most often routinely seen by a Paediatric Neurologist as part of clinical care in order to provide expert advice and management. In line with guidelines by the International Paediatric MS Group, demyelination clinics have been set up in several Tertiary Centres by paediatric neurologists with an interest in these conditions. This led to the UK and Ireland Paediatric CNS Inflammatory Demyelination Working Group being set up, providing a steering committee for future collaborative studies, networking, future direction, writing clinical guidelines and future grant applications. As a result, the majority of these children are seen in these specialist centres where they will be recruited.

Study aims and objectives

PUDDLS aims to establish if prognostic factors for relapse of CNS inflammatory demyelination (and hence risk of progression to MS) can be identified for UK children (Figure 1). PUDDLS is a prospective UK based study with the following objectives to:

1. Identify features (clinical, epidemiological, imaging, pathophysiolgical tests such as oligoclonal bands) that may predict which children are more likely to relapse and develop MS, whilst assessing the validity and utility of the new consensus definitions for childhood CNS inflammatory demyelination and of proposed MRI criteria.
2. Establish outcomes for children, for an initial period of up to five years depending on when the case was recruited (minimum 6 months follow up).
3. Describe disease modifying therapy usage, efficacy, and adverse effects.
4. Provide a platform for future a) identification of biological markers in MS, b) genetic studies and c) hypothesis driven biological studies; by storing blood and CSF samples already taken at the time of first demyelinating event (currently in 7 participating centres).
5. Ensure that long term outcomes of childhood demyelinating disease are as complete as possible by flagging patients with their consent with the NHS Information Centre [Medical Research Information Service (MRIS)] which will allow them to be traced in future via their G.P.s (currently in 7 selected centres).

Specific Hypotheses:

We wish to test the following *hypotheses* (as suggested by the IPMSSG [17]):

(i) Children who present with CIS are more likely to develop MS than children who present with ADEM

(ii) ADEM Children with prolonged steroid– dependent events (≥3 months) are more likely to develop MS than children with rapid recovery ADEM

(iii) Children with multiphasic ADEM compared to children with recurrent ADEM are more likely to develop MS.

(iv) Children with recurrent ADEM are more likely to develop MS than children with monophasic ADEM.

(v) MRI criteria (McDonald, KIDMUS) can be validated to distinguish between ADEM, ADEM variants, CIS, and MS

(vi) Identified future biomarkers with suggested prognostic significance, can be tested against PUDDLS outcomes

(vii)   Early treatment with disease modifying therapy in relapsing CNS Inflammatory Demyelination, reduces relapse rate and slows neurological disability progress.

(viii)   Environmental risk factors can be identified for children with first episode CNS inflammatory demyelination and MS.

New hypotheses will be added if suggested by publications by other centres prior to data analysis

Figure 1 PUDDLS Flowchart with link to epidemiological study.
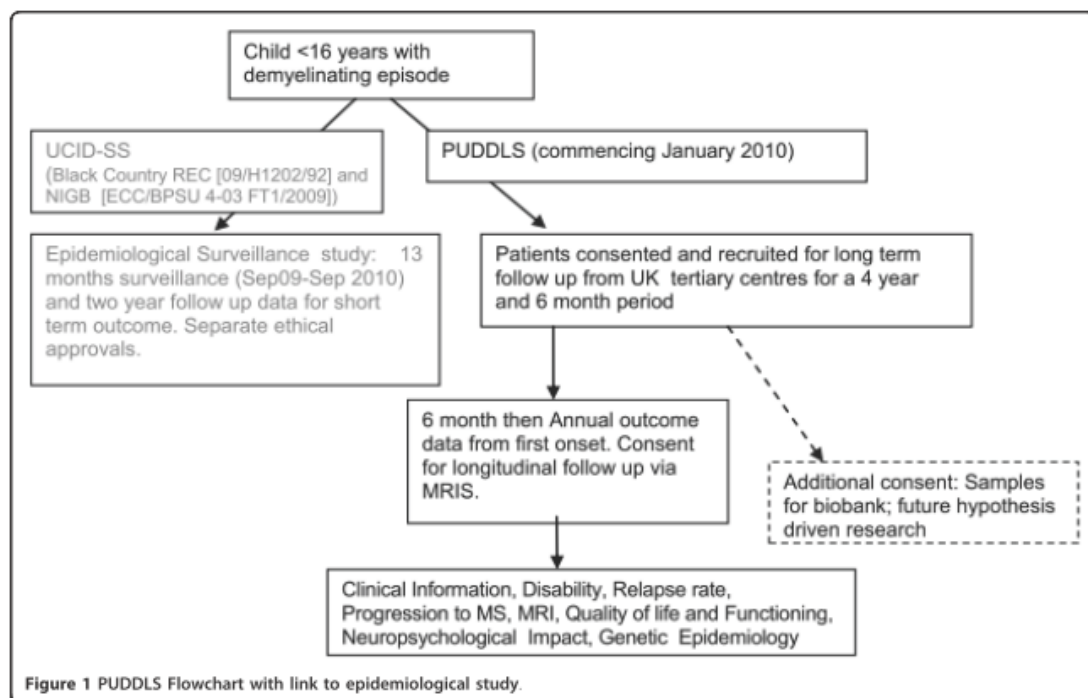
METHODS/ DESIGN

Case Definitions and Inclusion Criteria:

Children (younger than 16 years) experiencing first episode of clinical neurological events consistent with site specific inflammatory CNS demyelination and except in Optic Neuritis confirmed with white matter changes on MRI (table 1).

Table 55: Summarised definitions for CNS Inflammatory Demyelinating Disease

Condition	Definition
Acute Disseminated Encephalo-myelitis (ADEM)	A polysymptomatic clinical event with acute/subacute onset that must include encephalopathy (behavioural change or altered consciousness). (2) <u>MRI</u> Brain shows multifocal (usually diffuse bilateral lesions), predominantly involving white matter. • Relapsing ADEM: symptoms or signs within 3 months of initial onset of ADEM. IF a new event occurs ≥3 months later and ≥1 month after completing steroid treatment, it is defined as: • Recurrent ADEM: recurrence of initial symptoms without involvement of new clinical areas. • Multiphasic ADEM: New event, but involving new anatomical areas of the CNS.
Clinically Isolated Syndrome (CIS)	A first acute-clinical episode of CNS symptoms which may either be monofocal or multifocal, but does not include encephalopathy (except in brainstem syndromes). The <u>MRI</u> will show area of white matter demyelination. These include: ***Transverse myelitis***: weakness and/or numbness of both legs +/- arms, usually with maximal deficits 1 week after symptom onset supported by demyelination on MRI spine. ***Brainstem***, ***cerebellar***, and/or ***hemispheric*** dysfunction, supported by demyelination on MRI.
Optic Neuritis (ON)	Acute or subacute loss of vision and ≥1 of: relative afferent pupillary defect (unilateral cases), visual field deficit or scotoma, impaired colour vision, optic disc oedema, or abnormal visual evoked potentials. MRI is not necessary for diagnosis.
Neuro-myelitis Optica (NMO)	Must have: i. Optic neuritis <u>and</u> ii. Acute myelitis iii. Must have: Spinal MRI lesion extends over three or more segments **OR** iv. NMO antibody testing is positive. The brain MRI must not meet Multiple Sclerosis diagnosis criteria

Table 56: IPMSSG Multiple Sclerosis definition

Multiple Sclerosis (MS)	- Two or more **non ADEM** episodes of CNS demyelination separated in time (4 weeks) and space. For children aged >12 years:
	- Dissemination in space can be met if: <u>MRI</u> shows three of: 1) ≥ 9 white matter lesions or 1 gadolinium enhancing lesion, 2) ≥3 periventricular lesions, 3) One juxtacortical lesion, 4) an infratentorial lesion.
	<u>OR</u> abnormal CSF (oligoclonal bands or elevated IgG index) with 2 lesions on the <u>MRI</u> (one in the brain).
	- Dissemination in time can be met if: <u>MRI</u> shows new T2 or gadolinium enhancing lesions developing ≥3 months after initial event.

Exclusion criteria:

1. Leukodystrophies (e.g., metachromatic leukodystrophy, adrenoleukodystrophy) or mitochondrial disease
2. Proven CNS infection (e.g. bacterial meningitis, herpes simplex encephalitis, Lyme disease, HIV)
3. Radiation/chemotherapy associated white matter damage
4. Condition fulfilling criteria for CNS connective tissue disease e.g. lupus, vasculitis. The sole presence of antibodies associated with CNS connective tissue diseases is not sufficient for exclusion.

Relapses, MS, and Progression

A relapse is a new occurrence of neurological symptoms that lasted > 24 hours and stabilized or resolved either partially or completely. MS is defined in table 2 below. Progression of MS is a continuous worsening of symptoms and signs for > 6 months, ± superimposed relapses, either primarily (at onset of disease) or secondarily (after first relapse).

Design

PUDDLS is a observational cohort study with sample biobanking which will characterize the spectrum of CNS demyelinating syndromes, their outcomes, and possible progression to MS (Figure 2). Children will be recruited over a 4 year and 6 month study period and followed up. At recruitment an initial Case Report Form (CRF) will be completed by the PI/Research Nurse/Research Fellow. MRI copies and biological samples will be archived. An environmental questionnaire will be administered by telephone interview within three months of disease onset. Patient reported and proxy outcome questionnaires will be completed online at onset and at specified time intervals (figure 3). At six months and one year from onset, and then at yearly intervals, a follow-up CRF will be completed in clinic. A telephone interview will also be conducted at the same frequency to ask if the patient has

had a clinical relapse or hospital admission and to provide an opportunity to ask questions. Any significant concerns will be referred back to the GP or clinician in charge.

Figure 2 The 5 major study themes are represented in flow the Figure below.

Data Collection/procedure	At recruitment	6 months After onset	Yearly after first event	Additionally at relapse (s)
Information leaflets & consent/assent	×Δ			
First episode performa (CRF) [Δ]	× Δ			
Follow up/ Relapse performa (CRF) [Δ]		× Δ	× Δ	
MRI copies	× Δ	× Δ		× Δ
Sample Collection for biobanking	×			×
*Pediatric Quality of Life Inventory TM and Multidimensional Fatigue and Scale (10 minutes)	☺ ♣	☺ ♣	☺ ♣	
* Profile Of Neuropsychiatric Symptoms (10 minutes)	☺ ♣	☺ ♣	☺ ♣	
*Adaptive Behavior Assessment System II; conceptual + social skills (10 minutes)	♣	♣	♣	
*MSIS-29 (5-10 minutes)	☺ ♣	☺ ♣	☺ ♣	
Cognitive games (10 minutes)	☺	☺	☺	
Brief outcome telephone interview: check if relapses occurred (10 minutes)		Δ ♣	Δ ♣	

*Health Tracker® online
- Environmental Questtionaire: Telephone Interview with parent/carer (30-45 minutes) will also take place once during the study period within 6 months after disease onset.

× Neurologist Collaborator/ PI   ☺ Child   ♣ Parent/Carer   Δ Research Nurse/Research Fellow

Figure 3 Data and Outcome Collection Schedule Summary.

Patient recruitment and consent

Based on an expected incidence of 1-2/100,000 children, each Centre is expected to recruit approximately 10-15 cases/year over the 5 year length of the study, with a minimum of 6 months follow up. Children with CNS Inflammatory Demyelination are seen by Paediatric Neurologists with an interest in CNS Demyelination to provide expertise in diagnosis and management. Patients usually present to Neurologists' attention via the following routes:
- Presentation directly to Tertiary Centre
- Referral from Paediatric DGH Consultant for admission or an outpatients opinion
- MRI scans referred to weekly Tertiary Centre Neuroradiology meeting for an opinion (permission to approach the clinician for referral will be obtained).
- Shared care or outreach clinic

Patients will be ascertained via these available methods, and given or sent information leaflets before being consented (minimum 24 hours) to take part in the study. A website (www.childdemyelination.org.uk) is set up to provide newsletters and information regarding study progress, and up to date information on management directed at Paediatricians. If the patient or carer requests referral, normal clinical follow up patterns of care will be followed.

Currently in 7 centres, PIs will obtain consent from families presenting to their centres. The Paediatric Research Nurse at each site (0.1 WTE at each site, except lead Centre [Birmingham] to have 0.3 WTE) or the Research Fellow (Dr M Absoud) may also approach families directly to obtain consent. Appropriate agreements and contracts will be in place for the Research Fellow and Nurse as recommended by the National Institute for Health Research. Patients will be asked to consent to:
- Taking part in the study and l**ongitudinal follow up** via The National Health Service Information Centre [Medical Research Information Service (MRIS)]
- Storage of **Samples** (CSF, DNA, serum)
- Obtaining **MRI** copies and information from Hospital notes
- Sharing an anonymised dataset with the International Paediatric Study MS Group.

Data Collection and Outcome assessment

Data collection will take place at recruitment, 6 months after initial event, annually after initial event, and during clinical relapses (see Figure 3). Clinical follow ups for patients affected with CNS inflammatory demyelinating diseases will be part of clinical care, and no extra hospital visits will be required. Children and parents/carers will be able to fill in questionnaires from a secure online programme (Healthtracker TM). Access to a computer with privacy will be made accessible if needed during clinic visits. The Research Nurse will make contact with the family at the designated follow up times, to ensure they understand the research, ask about any relapses or investigations the child might have had, and discuss further queries.

The primary outcome measures will be (1) if the patient developed a clinical relapse, and (2) a diagnosis MS. Secondary outcome measures will include: Patient reported and proxy Quality of life, disease impact, neuropsychiatric & fatigue symptoms, conceptual & social adaptive behavioural functioning skills, MRI criteria, and objective EDSS disability scores (ie. EDSS>5.5, patient unable to walk without aid).

Case Report Forms (CRFs):

The CRFs have been adapted with permission after consultation with the International Group. The initial CRF (first episode) will be completed by the PI, the Research Fellow, or the Research Nurse with assistance from the PI. A condition specific targeted neurological history (using a check box questionnaire) would take place at the time of first demyelinating event. The event would be classified as either ADEM, CIS, or MS (see case definition). Data collected can broadly be categorised to:

a. Basic demographic data (ethnicity, place of birth, current residence)
b. Family history of MS or autoimmune disease
c. Demyelinating symptoms and signs (using tick box table)
d. Presence of behavioural disturbance or encephalopathy (to distinguish ADEM from CIS) at time of demyelinating event.
e. Information which might predict the subsequent development of recurrent ADEM, multiphasic ADEM, or MS, like details of the anatomic distribution (optic nerve or spinal cord, monofocal or multifocal distribution), CSF findings, serological and neuroimaging results.
f. Treatment (eg, steroids, immunoglobulins, intensive care) given.
g. Information as to whether the risk of future MS was given to the family.
h. Neurological examination, Kurtze EDSS scales, and functional status.

For **6** month and **annual** outcome data, follow up information will be obtained on neurological function and further demyelinating events (if these have occurred). We aim to collect 90% data within a window period of one month on either side of the designated follow up periods.

Healthtracker®; patient self report and proxy outcomes

PUDDLS will use Healthtracker® which is a sophisticated, user-friendly, UK, and web-based assessment system launched with Department of Health support in 2008. It comprises a suite of questionnaires and test games for children and their carers, and not for investigator use. These allow accurate measures of change across a wide range of symptoms, side-effects, psychological functions and quality of life. Assessments can be home-based for convenience and lower costs. This helps circumvent the many practical difficulties associated with long-term assessment of chronic diseases.

Health related Quality of Life (QOL)
- Generic QOL: Paediatric Quality of Life Inventory TM;
Generates physical, psychological, and total score.
  o Self report for ages 5-25 years.
  o Parent report for ages 2-25 years.
- Disease specific QOL: Multiple Sclerosis Impact Scale-29 version 2 (MSIS-29 v2)
Generates physical, and psychological scores.

- o   Self report for children 5 years -adulthood
- o   Parent report.

Fatigue
-   Paediatric Quality of Life Inventory TM; Multidimensional Fatigue Scale
    - o   Self report for children 5-25 years
    - o   Parent report; for children 2- 25 years

Neuropsychiatric Symptoms
-   Profile Of Neuropsychiatric Symptoms (PONS)
    - o   Self report for children 5-16 years
    - o   Parent report

Functioning ; Adaptive behavioural skills
    - o   Adaptive Behaviour Assessment System II (ABAS II).
-   Parent report for children 5 years –adulthood. Two out of the three domains will be used:
    - (iii)   Conceptual skills: communication, functional academics, and self-direction skills areas
    - (iv)   Social skills: Social, and leisure skills areas

Cognitive
    - o   Two Healthtracker online games played by children aged 5-16 years that aim to measure memory, attention and concentration. These are embedded in between questionnaires.
    - o   Online D2 test game for participants aged 9 years- 60 years. The D2 Test measures processing speed and quality of performance of individuals, allowing for a neuropsychological estimation of individual attention and concentration performance.

Environmental Questionnaire:

One off telephone interview (30-45 minutes) with parent/carer to be conducted during study period within three months of disease onset if direct hospital contact whilst inpatient has not been achieved. Only once further funding is gained, case controls for administering only the environmental questionnaire will be ascertained via a 'buddy system' to the child who is age and sex matched. No other involvement of controls will be required.

MRI criteria:

Routine patient MRIs will be collected in order to apply proposed criteria (such as McDonald, KIDMUS) that the study team can validate against PUDDLS outcomes. Data will be collected using a standardised data collection performa with agreed definitions designed by Neuro-radiology collaborators (available on request). MRIs will be randomly evaluated by one of four Neuroradiologists blinded to presentation and clinical features. Inter-rater reliability will be assessed.

Biobank sample collection:

Samples and Procedures:
Additional informed consent will be obtained to store sera, DNA, and CSF collected during routine clinical care at first onset of a CNS demyelinating event, and then at future hospital visits if clinical relapses occur. This will be done in accordance with the Human Tissue Act (HTA, 2004). Currently designated laboratories in each of the seven establishments hold appropriate HTA licences and would be responsible for storage:
(http://www.hta.gov.uk/licensingandinspections/listoflicensedestablishments.cfm)
1. Alder Hey Children's NHS Foundation Trust
2. Birmingham Children's Hospital
3. Frenchay Hospital
4. Great Ormond Street Hospital
5. Guy's & St Thomas' Hospitals, Cellular Pathology
6. John Radcliffe Hospital
7. Nottingham University Hospitals NHS Trust

Sample collection, transport and storage will be undertaken using standard SOPs and be based at collaborating centres as appropriate.

There will be no additional venepuncture or lumbar puncture procedures for the child beyond those required for routine clinical care. Informed consent will be required, for extra volumes to be collected during these procedures for the study. Residues of CSF and blood already taken as part of the clinical management of the patient, will also be used for future research investigations and to supplement the specimen archive. For each patient at least one CSF sample and two blood samples will be required. Clinicians will be encouraged to follow existing guidelines for the investigation of CNS demyelinating disorders (17,18) and as updated in the future

Confidentiality
Samples will be stored pseudoanonymised in HTA approved labs, and linked with the clinical data by the unique PUDDLS number. Any information that is likely to identify participants (such as name, address, date of birth) will be removed from samples. Personal identifiers are kept separately under strict control with restricted access in secured cabinets, at the Institute of Child Health, Birmingham Children's Hospital in a secure locked area. Access to data is limited to the Chief and Principal Investigators. The study administrator at Birmingham Children's Hospital will ensure pseudo-anonymous tracking of the samples, solely for the purposes of linkage once they are collected as informed by the Principal Investigator. The location, nature and date of samples will be recorded on the database

Future research
Separate funding will be sought for the biological/genetic sample studies and a further five year longitudinal follow up, once sufficient samples and clinical data has been collected. The details of the studies are beyond the scope of this protocol but we have identified future potential studies of sufficient scientific validity to ethically justify the storage of human samples. Collaborations with international experts and leaders in the field will maximise yield of investigations, and ensure a thorough review process:

The PUDDLS Biological Studies Steering Group will consider any future studies, and follow the agreed guidelines for study selection (***available on request***). Once studies are deemed of sufficient quality, and depending on the strand of study the group will collaborate with the experts in their fields and with the International Paediatric Multiple Sclerosis Study Group (IPMSSG)

Expected Numbers:

Based on an expected incidence of 1-2/100,00 children, the expected recruitment over the initial 5 year study period is 400-450 cases (12-13/year in every Centre).

Statistics and data analysis

Descriptive statistics (with confidence intervals where appropriate) will be used to summarise the key components of the database. Univariate associations between potential prognostics factors and potential confounders and with MS diagnosis or other CNS demyelinating episodes; outcomes. These associations will be further explored in logistic regression models that will allow for control of confounding factors. Factors associated with early occurrence of second episodes will also be explored and Cox models will be used if the proportional hazards assumption is met. Life table analysis methods will be used to calculate primary outcome time points. SPSS (v.17.0) statistical software will be used for data analysis.

Research and development procedures

Research & Development (R&D) approval from each participating NHS Trust will be obtained prior to recruitment. Principal investigators will follow rules of data protection ethics and confidentiality

Longer term follow up:
To ensure that long term outcomes of childhood demyelinating disease can be identified by flagging patients with their consent via the NHS Information Centre (MRIS) and NHS Central Register which will allow them to be traced in the future via their G.P.s. We will consent patients for long term follow-up.

Data Handling and Integrity

- Each patient enrolled will be assigned a unique PUDDLS study identification number. This number will be used in all future correspondence between the study centre and principal investigators.

- Principal investigators will be responsible for the security of data at each local site according to their employing authorities' rules and regulations. Investigators will ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, and applicable regulatory requirements.

- Patient identifiable information (name and address) will be sent to the study office on only one occasion (initial case report form) by secure fax. The original signed consent form to participate in the study will be kept in the patient's medical records unless required otherwise by local regulations, and a copy kept securely in the site file.

- At the central study office (ICH, Birmingham Children's Hospital), all patient identifiable study data will be stored in locked filing cabinets. Identifiable patient data will be separated from the clinical data and linked with a unique study code. Clinical data used for research may also include patient identifiable data, e.g. date of birth, sex, that are also important for the data analysis, linkage during follow up, and to answer the research questions. These cannot be removed from the questionnaire and will be stored for 30 years in secure archives (MRC guidelines). Only pseudo-anonymised clinical data only will be entered into the electronic study database for analysis. Case report forms will be kept in the site file in a secured locked cabinet, and a copy will be sent to the Central study office at the Institute of Child Health, Birmingham Children's Hospital.

- Database Information

(i)   Clinical Information

The research nurse, data administrator, and/or the research fellow will enter and maintain the clinical information for all study participants from within the Institute of Child Health (ICH), Birmingham Children's Hospital. The database will be anonymised. CRFs will be sent to the study team on paper. This has the added benefit of providing consistency of data entry, allowing for more complete and accurate set of data for long term analysis. This database will use the PUDDLS code only. The data base will be password protected, backed up by the ICH server backup daily, and encrypted for added protection. The database will be accessed according to Trust policies and procedures.

(ii)   Healthtracker TM

Healthtracker is hosted with Rackspace on a single server running the Microsoft Windows Server 2003 Standard Edition operating system. Rackspace ensures the server is continuously updated and has all the latest service packs and security patches. The server itself houses a Dual-Core AMD Opteron processor running at 2.20 GHz with 4.0 GB of RAM. It has three 73GB SCSI hard drives in a RAID 5 configuration offering 140GB of usable storage. The server acts as both the web and database server running Internet Information Services (IIS) and SQL Server 2005 Standard Edition.

Both the admin and non-admin websites use SSL 128bit encryption to ensure data is securely encrypted between requests. The websites are written in C# and run under the Microsoft .Net 2.0 framework. HTML and cascading style sheets are used in both sites to apply common styling. All database transactions are performed via stored procedures (there is no

in-line SQL). Flash is used to provide some questionnaire and game content to the child portion of the non-admin website. XML web services are used to send and receive information to and from these components. All data in the system is stored in a single SQL Server database and therefore can be exported in any format facilitated by SQL Server. Alternatively custom exports can be written.

Healthtracker (HT) Results are generated in real time and can reflect symptom trends/treatment efficacy/or changes over time. The program has been designed with the ability to analyse large amounts of longitudinal data with inbuilt real-time Bayesian/Neural Net algorithms. This system allows testing of hypothesis as new data comes in. The online presentation of HealthTracker has already meant that rapid acquisition of data for norming, or comparing new measures with existing ones is possible. Non-linear mixed effects modelling will be used to generate estimates of expected recoveries. Data from HT will also be exported via an excel spreadsheet for the research team to analyse. Item analysis of questionnaires will be via Rasch analysis, utilising the WINSTEPS TM statistical software.

- Data protection, security and confidentiality will be implemented according to the UK Data Protection Act 1998 and each Trust's own Information Governance Policy.

LIST OF ABBREVIATIONS

ADEM: Acute Disseminated Encephalomyelitis
CNS: Central Nervous System
CIDD: CNS Inflammatory Demyelinating Disease
CRF: Case Report Form
CSF: Cerebrospinal Fluid
EDSS: Expanded Disability Status Scale
Health Tracker®: A web-based assessment system which comprises a suite of questionnaires and test games for children. These allow accurate measures of change across a wide range of symptoms, side-effects, psychological functions and quality of life. Assessments can be home-based for convenience and lower costs.
HTA: Human Tissue Act 2004
(http://www.opsi.gov.uk/acts/acts2004/ukpga_20040030_en_1)
IPMSSG: International Paediatric Multiple Sclerosis Study Group
Life-H: Assessment of Life Habits Questionnaire
MCRN: Medicines for Children Research Network
MRIS: Medical research Information Service.
MS: Multiple Sclerosis
MSIS-29: The Multiple Sclerosis Impact Scale; Parent report version
NIHR: National Institute for Health Research
NMO: Neuro-myelitis Optica
ON: Optic Neuritis
PedsQL: Paediatric Quality of Life Inventory TM
PUDDLS: Paediatric UK Demyelinating Disease Longitudinal Study
SDQ: Strengths and Difficulties Questionnaire
SOP: Standard Operating Procedure
TM: Transverse Myelitis
UCID-SS: UK and Ireland Childhood Inflammatory Demyelination Surveillance Study
UKCRN: UK Clinical Research Network
UKCNRC: UK Children's Neurological Research Campaign; Provides neurology network and study management support.
WTCRF: Wellcome Trust Clinical Research Facility

5. Cochrane's RevMan v5.1 and NQuery metanalysis and sample size estimations using data from the TRANSFORMS and FREEDOMS trials.

TRANSFORMS

Annualised relapse rate for Active Comparator= 0.33 (SD 0.9) n=431

Annualised relapse rate for Fingolimod= 0.18 (SD 0.5) n=854

FREEDOMS:

Annualised relapse rate for Placebo= 0.40 (SD 0.8)   n=418

Annualised relapse rate for Fingolimod= 0.17   (SD 0.5)   n=840

Figure 1: To conduct an active RCT as in TRANSFORMS and assuming a similar risk ratio (0.62) for relapse in the study period and a similar event number, a sample size (equal numbers in both arms) of 436 children is required (power 80% and alpha 5%).

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 New Subgroup						
FREEDOMS	234	854	227	418	55.7%	0.50 [0.44, 0.58]
TRANSFORMS	160	849	132	431	32.0%	0.62 [0.50, 0.75]
Subtotal (95% CI)		1703		849	87.7%	0.54 [0.49, 0.61]
Total events	394		359			
Heterogeneity: Chi² = 2.59, df = 1 (P = 0.11); I² = 61%						
Test for overall effect: Z = 10.32 (P < 0.00001)						
4.3.2 Childhood studies						
Child Study Exp vs ACtive	0	0	0	0		Not estimable
Child Study Exp vs Active	42	218	67	218	12.3%	0.63 [0.45, 0.88]
Child Study Exp vs placeb	0	0	0	0		Not estimable
Subtotal (95% CI)		218		218	12.3%	0.63 [0.45, 0.88]
Total events	42		67			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.72 (P = 0.007)						
Total (95% CI)		1921		1067	100.0%	0.56 [0.50, 0.62]
Total events	436		426			
Heterogeneity: Chi² = 3.31, df = 2 (P = 0.19); I² = 40%						
Test for overall effect: Z = 10.54 (P < 0.00001)						
Test for subgroup differences: Not applicable						

Figure 2:
sample size for a placebo RCT with same assumptions is n=134

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 New Subgroup						
FREEDOMS	234	854	227	418	46.2%	0.50 [0.44, 0.58]
TRANSFORMS	160	849	132	431	26.5%	0.62 [0.50, 0.75]
Subtotal (95% CI)		1703		849	72.7%	0.54 [0.49, 0.61]
Total events	394		359			
Heterogeneity: Chi² = 2.59, df = 1 (P = 0.11); I² = 61%						
Test for overall effect: Z = 10.32 (P < 0.00001)						
4.3.2 Childhood studies						
Child Study Exp vs placeb	24	89	24	45	4.8%	0.51 [0.33, 0.78]
Subtotal (95% CI)		707		463	27.3%	0.66 [0.55, 0.80]
Total events	158		152			
Heterogeneity: Chi² = 2.42, df = 2 (P = 0.30); I² = 17%						
Test for overall effect: Z = 4.19 (P < 0.0001)						
Total (95% CI)		2410		1312	100.0%	0.58 [0.52, 0.64]
Total events	552		511			
Heterogeneity: Chi² = 8.13, df = 4 (P = 0.09); I² = 51%						
Test for overall effect: Z = 10.88 (P < 0.00001)						
Test for subgroup differences: Not applicable						

Figure 3: If the event rate is higher in children than in adults (eg. by 50%) the required sample size for an active RCT is n=248

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95%
4.3.1 New Subgroup						
FREEDOMS	234	854	227	418	56.8%	0.50 [0.44, 0.58]
TRANSFORMS	160	849	132	431	32.6%	0.62 [0.50, 0.75]
Subtotal (95% CI)		1703		849	89.4%	0.54 [0.49, 0.61]
Total events	394		359			
Heterogeneity: Chi² = 2.59, df = 1 (P = 0.11); I² = 61%						
Test for overall effect: Z = 10.32 (P < 0.00001)						
4.3.2 Childhood studies						
Child Study Exp vs ACtive	0	0	0	0		Not estimable
Child Study Exp vs Active	35	124	57	124	10.6%	0.61 [0.44, 0.86]
Child Study Exp vs placeb	0	0	0	0		Not estimable
Subtotal (95% CI)		124		124	10.6%	0.61 [0.44, 0.86]
Total events	35		57			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.82 (P = 0.005)						
Total (95% CI)		1827		973	100.0%	0.55 [0.50, 0.62]
Total events	429		416			
Heterogeneity: Chi² = 3.10, df = 2 (P = 0.21); I² = 36%						
Test for overall effect: Z = 10.65 (P < 0.00001)						

Figure 4: Assuming that MS is the same in adults as in children so that adult data is considered replicable in children but additional paediatric data is collected to perform a planned metanalysis of the TRANSFORMS + FREEDOMS + paediatric RCT, the calculated sample size is n=183 (121 experimental arm; 62 active arm).

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 New Subgroup						
FREEDOMS	234	854	227	418	60.4%	0.50 [0.44, 0.58]
TRANSFORMS	160	849	132	431	34.7%	0.62 [0.50, 0.75]
Subtotal (95% CI)		1703		849	95.0%	0.54 [0.49, 0.61]
Total events	394		359			
Heterogeneity: Chi² = 2.59, df = 1 (P = 0.11); I² = 61%						
Test for overall effect: Z = 10.32 (P < 0.00001)						
4.3.2 Childhood studies						
Child Study Exp vs ACtive	0	0	0	0		Not estimable
Child Study Exp vs Active	23	121	19	62	5.0%	0.62 [0.37, 1.05]
Child Study Exp vs placeb	0	0	0	0		Not estimable
Subtotal (95% CI)		121		62	5.0%	0.62 [0.37, 1.05]
Total events	23		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.78 (P = 0.07)						
Total (95% CI)		1824		911	100.0%	0.55 [0.49, 0.61]
Total events	417		378			
Heterogeneity: Chi² = 2.86, df = 2 (P = 0.24); I² = 30%						
Test for overall effect: Z = 10.44 (P < 0.00001)						
Test for subgroup differences: Not applicable						

Figure 5: Annualised relapse rate: Fingolimod vs Placebo and Avonex- Rate ratio (Generic inverse variance)

Study or Subgroup	Rate Ratio	SE	Weight	Rate Ratio IV, Fixed, 95% CI
FREEDOMS	-0.43	0.04	75.4%	-0.43 [-0.51, -0.35]
TRANSFORMS	-0.55	0.07	24.6%	-0.55 [-0.69, -0.41]
Total (95% CI)			100.0%	-0.46 [-0.53, -0.39]
Heterogeneity: Chi² = 2.22, df = 1 (P = 0.14); I² = 55%				
Test for overall effect: Z = 13.23 (P < 0.00001)				

Figure 6: Annualised relapse rate: Fingolimod vs Placebo and Avonex- Mean Difference

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
FREEDOMS	0.17	0.5	854	0.4	0.8	418	54.4%	-0.23 [-0.31, -0.15]
TRANSFORMS	0.18	0.5	840	0.33	0.9	431	45.6%	-0.15 [-0.24, -0.06]
Total (95% CI)			1694			849	100.0%	-0.19 [-0.26, -0.13]
Heterogeneity: Chi² = 1.60, df = 1 (P = 0.21); I² = 37%								
Test for overall effect: Z = 6.14 (P < 0.00001)								

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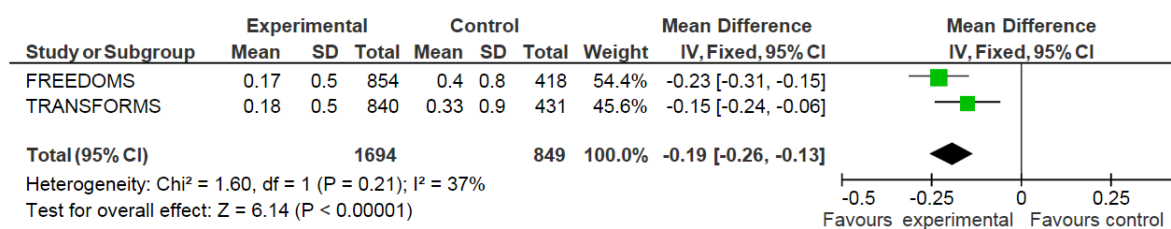
Figure 7: Disability Progression (3 months): Fingolimod vs Placebo and Avonex

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FREEDOMS	147	854	101	418	75.0%	0.71 [0.57, 0.89]
TRANSFORMS	53	849	34	431	25.0%	0.79 [0.52, 1.20]
Total (95% CI)		1703		849	100.0%	0.73 [0.60, 0.89]
Total events	200		135			

Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 3.09 (P = 0.002)
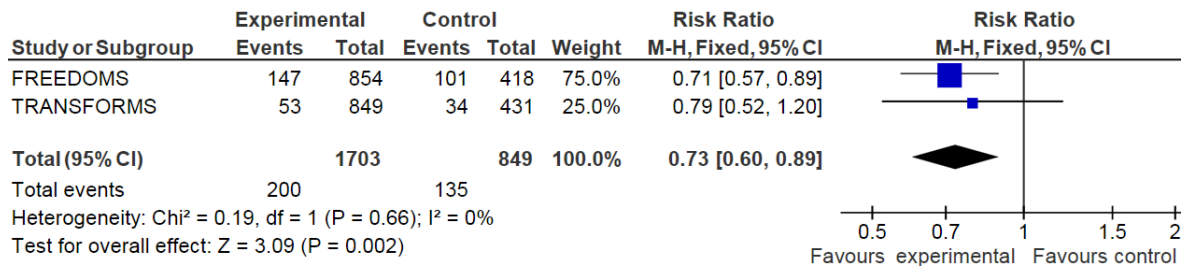
Figure 8: New or enlarged T2 lesions: Fingolimod vs Placebo and Avonex

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FREEDOMS	345	707	267	339	58.0%	0.62 [0.56, 0.68]
TRANSFORMS	350	722	196	361	42.0%	0.89 [0.79, 1.01]
Total (95% CI)		1429		700	100.0%	0.73 [0.68, 0.79]
Total events	695		463			

Heterogeneity: Chi² = 22.71, df = 1 (P < 0.00001); I² = 96%
Test for overall effect: Z = 8.07 (P < 0.00001)
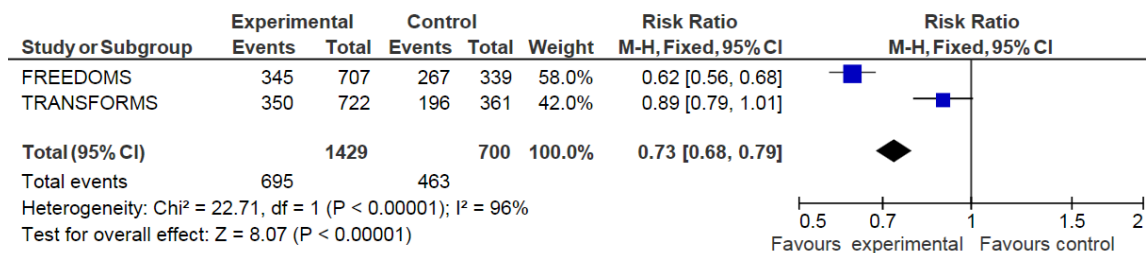
Figure 9: New T2 lesions mean difference

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
FREEDOMS	2.5	7.2	370	9.8	13.2	339	17.0%	-7.30 [-8.89, -5.71]
TRANSFORMS	1.7	3.9	372	2.6	5.8	361	83.0%	-0.90 [-1.62, -0.18]
Total (95% CI)			742			700	100.0%	-1.99 [-2.64, -1.33]

Heterogeneity: Chi² = 51.97, df = 1 (P < 0.00001); I² = 98%
Test for overall effect: Z = 5.96 (P < 0.00001)
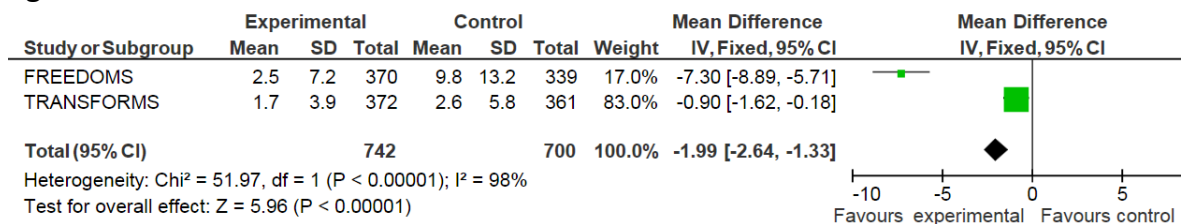
Figure 9: New GAD lesions: Fingolimod vs Placebo and Avonex

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FREEDOMS	73	712	116	322	63.6%	0.28 [0.22, 0.37]
TRANSFORMS	68	727	68	354	36.4%	0.49 [0.36, 0.66]
Total (95% CI)		1439		676	100.0%	0.36 [0.29, 0.44]
Total events	141		184			

Heterogeneity: Chi² = 6.71, df = 1 (P = 0.010); I² = 85%
Test for overall effect: Z = 10.13 (P < 0.00001)
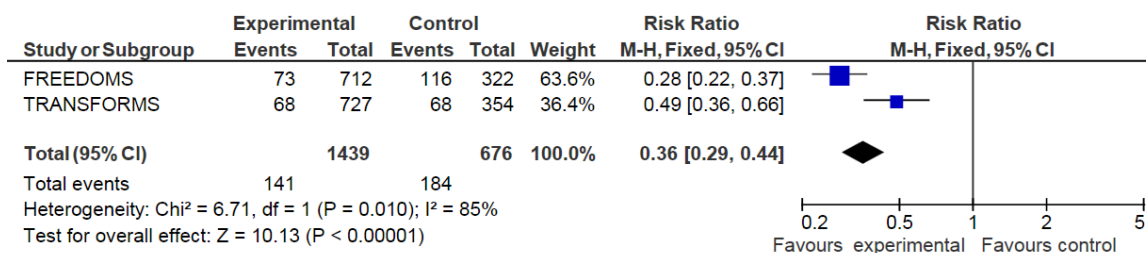
Figure 10: Brain Volume: Fingolimod 0.5 vs Placebo and Avonex

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
FREEDOMS	-0.15	0.075	30.8%	-0.15 [-0.30, -0.00]
TRANSFORMS	-0.14	0.05	69.2%	-0.14 [-0.24, -0.04]
Total (95% CI)			**100.0%**	**-0.14 [-0.22, -0.06]**

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
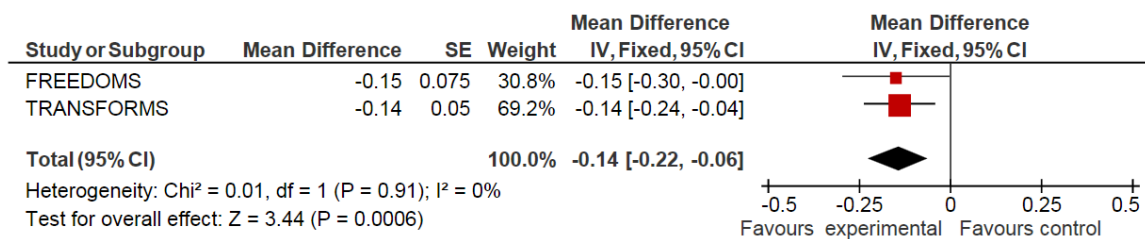Test for overall effect: Z = 3.44 (P = 0.0006)

Table 1: Sample size calculation based on MRI:

Mean(SD) new or enlarged lesions on T2-weighted images for (TRANSFORMS data):
Interferon B1a mean (SD): 2.6 (5.8)- n=431
Fingolimod 0.5mg mean (SD): 1.7 (3.9)- n=429

Using a two group Satterthwaite t-test with two sided α of 0.050:

Total estimated sample size=564 (282 in each group) will have 80% power to detect a difference in means of 0.9

Using the negative binomial distribution assuming a relatively conservative inflation of the variance over the mean by a factor of 2 (dispersion parameter (k) of 2:

A total estimated sample size=430 (215 in each group) will have 80% power to detect a difference in means of 0.9 new lesions.

6. Sample size calculations for childhood studies in multiple sclerosis and transverse myelitis

Table 1: RCT sample sizes based on relapse rate during the first year after CIS; data in Chapter 3.3. Sample sizes calculated using negative binomial model with an estimated dispersion Index (k) = 0.9

Based on baseline relapse rate	Number of new relapses in 1 year in active comparator (30% efficacy)	Number of new relapses in 1 year in oral drug (50% efficacy)	Total sample size required for 80% power / binomial	Total sample size required for 90% power/ binomial	Total sample size required for 80% power / T-test	Total sample size required for 90% power/ T-test
1.15	0.805	0.575	658	886	594	796
0.85	0.595	0.425	804	1082	1088	1456
0.60	0.42	0.3	1036	1384	2182	2920

Dispersion parameters (k) calculated manually using STATA v10 negative binomial distribution function.

Study Data (n= sample size)	Dispersion parameter (k)	Lower 95% CI	Upper 95% CI
Absoud thesis (n=38)	0.68	0.38	1.21
Fingolimod 0.5mg TRANSFORMS(n=429)	0.80	0.24	2.70
Avonex TRANSFORMS(n=431)	1.13	0.66	1.93

k - This is the estimate of the dispersion parameter. If the dispersion parameter equals zero, the data reduces to the simpler poisson distribution. If the dispersion parameter, **k**, is significantly greater than zero than the data are over dispersed.

Sample size and power analyses details for proposed TM trial

The primary intention to treat analyses will compare the control arm verses the intervention arm at 24 weeks post-randomisation. Allowing for 10% attrition (n=18), an overall sample size of 188 participants, 94 in each group, (randomised 1:1 to control arm: intervention arm) would provide 90% power to detect a 25% difference in the proportion of 2 point improvement or greater on the ASIA scale for the control verses intervention comparisons.

Note: this equates to an effect size of 0.500, as a secondary outcome I will consider the total motor score as a continuous measure (0-100). There will be 90% power to detect a difference between the control and treatment arms of a minimal effect size of 0.5. The Fleiss with continuity correction formula and method was used to calculate sample size and assumptions (openepi software version 2·3·1, www.openepi.com) (201). There is little evidence in acute transverse myelitis to summarise this is terms of variance and mean location. As a working example I believe that a 20 point difference will be of clinical significance. This trial has 90% power to see a difference between the control and intervention arms of 20 points or great , considering a pooled standard deviation as variable as 40.

The significance level will be 5% (2-sided) for main and secondary analyses. Estimates and confidence intervals will be needed for differences over treatment groups. Sensitivity analyses will assess the robustness of conclusions to missing outcome data and to departures from randomised treatment.

Analyses of effectiveness will be pragmatic, based on the intention-to-treat sample, and utilising all available follow-up data from all randomized patients. The models will include covariates; treatment group (control or intervention) and the stratification factors site and

status (adult or child). Where outcome variables have a baseline measure, this will be controlled for in the associated outcome analyses to allow for pre treatment differences.

All analysis will be repeated considering status (adult or child) as a moderator and interacted will treatment group (control or intervention), allowing estimates of treatment effect in the adult and child populations to be summarised.

The main objective of the statistical analyses will be to assess the effect of the intervention model on the primary outcome. Herein I will dichotomise the participant population in to those who are responders (a 2 point improvement or great from baseline on the ASIA scale) and non-responders. A generalised linear mixed-effects model will be utilised for the analyses, specifying a logistic regression.

There is expected to be missing data in the post treatment outcomes variables, as participants discontinue treatment and drop out of the study (lost to follow- up). The LMM analyses are based on maximum likelihood and will provide valid inferences under the missingness mechanism; missing at random (MAR).

Treatment effects on secondary outcomes will be also using a LLM, specified in the same way as the primary model, using generalisations of the linear mixed model to allow for non-normal data where necessary.

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