

## BRITISH PAEDIATRIC SURVEILLANCE UNIT

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### CNS INFLAMMATORY DEMYELINATING DISEASE

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#### Background

Acquired CNS inflammatory demyelinating diseases are rare disorders manifesting in childhood but may culminate in physical and cognitive disability or ultimately be diagnosed as Multiple Sclerosis (MS) [1]. Children with MS present with a demyelinating episode involving single or multiple symptoms prior to developing a second event (majority usually within two years) to then meet criteria for MS diagnosis. At first presentation of a demyelinating event, children are diagnosed with an acute disseminated encephalomyelitis (ADEM), optic neuritis, transverse myelitis, or another clinically isolated syndrome (CIS). It is not clear at the onset of symptoms which of these children will go on to develop MS.

There is evidence that 5% of Multiple Sclerosis (MS) cases manifest in childhood (2). The available literature, however, is limited to small case series and larger retrospective reviews of established adult MS populations (3). The true incidence of childhood demyelinating disease and MS is unknown, and the subject of recent international interest (4) and research (International Paediatric MS Study Group, [www.ipmssg.org](http://www.ipmssg.org)). This group recently published consensus definitions of paediatric demyelinating disorders and MS to facilitate uniformity in future research (5). Evidence from adult cohorts shows that the incidence and sex ratios of MS are changing and that children of immigrants are at higher risk of developing MS (6). Paediatric populations should be in the vanguard of such changes and may reflect trends yet to be observed in adult cohorts. Genetic epidemiology to date supports the dual role of "nature and nurture" in MS pathobiology (6), and incidence rates differ geographically.

There is an urgent need for prospective population based studies with international collaboration, to further understand clinical, radiological, and pathobiological features as well as outcome of childhood onset demyelinating disease and MS. To our knowledge, this will be the first nationwide study since the proposal of new consensus definitions. Unravelling the epidemiology and natural history of paediatric demyelinating disorders is crucial as there is currently no available biomarker that fulfils the criteria of a surrogate endpoint in MS in children. For acute demyelinating illnesses, and relapses or attacks of MS, corticosteroids are the mainstay of treatment. Important newer weapons against MS are "disease modifying agents", such as interferon and glatiramer acetate that decrease relapses by modifying the immune system. There appears to be benefit in the early initiation of these therapies in adults (7), however, little is published on their use in children. The determination of the outcome of the first 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 challenging but critical to quantify the risk to benefit ratio of any intervention. Furthermore, identifying the incidence of paediatric acquired demyelinating disorders and MS in the UK and Ireland has major implications when planning service provisions, where there is evolving evidence of lack of awareness, and patchy service provision (Paediatric MS meeting, London November 2007).

**Coverage:** United Kingdom and the Republic of Ireland.

**Duration:** Surveillance: September 2009 – September 2010 (13 months).  
Outcome: one and two year questionnaires (September 2010-September 2012).

**Objectives:** The specific aims of the project are, within the UK and Ireland, to:

1. Determine the incidence of childhood acquired demyelinating disease and MS.
2. To report clinical features, and distribution by age, sex and ethnic group.
3. To identify the frequency of proposed predictors (clinical and radiological) for MS in children.
4. To establish short term outcomes and recurrence after a first demyelinating event in children.
5. Determine whether these children can be classified according to the new international classification and further characterise those that cannot.
6. Increase awareness amongst Paediatricians and describe current practices and treatments offered.

### Case Definition

#### Including:

Children under 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 defined below:

Acute Disseminated Encephalomyelitis (ADEM)	A clinical event (subacute or acute, poly-symptomatic, <b>must include encephalopathy</b> ) due to a presumed inflammatory or demyelinating cause affecting multifocal areas of the CNS, <i>and</i> MRI white matter changes.
Clinically Isolated Syndrome (CIS)	A <b>first</b> acute clinical episode of CNS inflammatory demyelination (monofocal or multifocal but <b>does not include encephalopathy</b> ) <i>and</i> MRI white matter changes.
Transverse Myelitis	Weakness and/or numbness of both legs (with or without involvement of arms) <i>and</i> supported by demyelination on MRI of spine.
Optic Neuritis	Subacute/acute loss of vision with a presumed demyelinating origin.
Neuromyelitis Optica (NMO)	Optic neuritis and associated myelitis.

**Excluding:** Children presenting with their **second or subsequent** demyelinating episode.

**Reporting Instructions** Please report any cases with a **first** demyelinating episode meeting the case definition and seen in the past month.

**Analytic Definitions** Analytic Case Definitions will be those recommended by the International Paediatric MS Study group. These can be viewed on: <http://bpsu.inopsu.com>

**Methods** Clinicians will be asked to complete a brief questionnaire seeking information on diagnosis, clinical features, and also to provide a copy of the MRI. An expert panel will meet on a quarterly basis to review cases reported. Clinicians will be asked to report outcomes using questionnaires sent at one and two years following diagnosis. Information on the recurrence of demyelinating event (if occurred), death, current functional status and treatment will be sought. Cases will be ascertained by the British Paediatric Surveillance Unit (BPSU) and British Ophthalmological Surveillance Unit (BOSU). British Paediatric Neurology Association members, who are consultants and who do not receive the 'orange card' will be added on for the duration of the study. Monthly notification cards will be sent to all registered Consultant Paediatricians, Paediatric Neurologists, and Ophthalmologists.

**Ethics Approval** The study has Black Country Research Ethics Committee (09/H1202/92) and NIGB Ethics and Confidentiality Committee approvals (ECC/BPSU 4-03 [FT1] /2009).

**Funding** Multiple Sclerosis Society and Action Medical Research Charities.

### References

1. Ness JM et al.:2007: Clinical features of children and adolescents with multiple sclerosis. *Neurology*: Apr 17; 68(16 Suppl 2):S37-45.
2. Mikaeloff Y et al.: 2004: First Episode Of Acute CNS Inflammatory Demyelination In Childhood: Prognostic Factors For Multiple Sclerosis And Disability. *Journal Paediatrics* 144:246-52.
3. Duquette P et al: 1987: Multiple sclerosis in childhood: clinical profile in 125 patients: *J Pediatr. Sep*; 111(3):359-63.
4. Banwell B et al.: 2009: Incidence of acquired demyelination of the CNS in Canadian children. *Neurology*, Vol. 72, pp. 232-9
5. Krupp LP et al: 2007: Consensus definitions proposed for pediatric multiple sclerosis and related disorders for the International Pediatric MS Study Group. *Neurology* 68(Suppl 2) April 17.
6. Ebers GC et al.: 2008: Environmental factors and multiple sclerosis. *Lancet Neuro*, Vol. 7, pp. 268-77.
7. Coyle PK et al.: 2008: Early treatment of multiple sclerosis to prevent neurologic damage. *Neurology*, Vol. 71(24 Suppl 3), pp. S3-2.