PROTOCOLS

Acquired demyelinating syndromes of the central nervous system

Principal investigator

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Background

Multiple sclerosis (MS) is a chronic neurological disorder defined by recurrent episodes of central nervous system (CNS) demyelination, ultimately culminating in physical and cognitive disability. While it is rare in the paediatric population, MS in children is likely to have a profound impact on their lifetime academic, social, and vocational achievements. The advent of disease-modifying therapies for MS and the recent evidence of improved long-term outcome, associated with early initiation of therapy, emphasize the need for prompt diagnosis and coordinated care for children affected with MS.

Several barriers currently exist to the prompt diagnosis of MS in children: (1) Knowledge of the clinical symptoms of paediatric MS is limited; (2) a diagnosis of MS is often not considered in children since MS is widely viewed as an exclusively adult-onset disease; (3) systematic clinical surveillance of children at risk for MS (i.e., children who have experienced a single attack of CNS demyelination) is currently not practiced in most centres; and (4) clinical, epidemiological, or biological risk markers predictive of MS have yet to be defined.

The varied clinical phenotypes of initial acute CNS demyelination, termed clinically isolated syndromes (CIS), include optic neuritis, transverse myelitis, hemisensory or hemi-motor syndromes, cerebellar or brainstem dysfunction, alone (mono-symptomatic CIS), in combination (polysymptomatic CIS), or associated with encephalopathy (acute disseminated encephalomyelitis, ADEM). The ability to predict whether CIS in an individual patient represents a monophasic disorder

or is the harbinger of the recurrent demyelination that characterizes MS remains an ongoing challenge. The disorder known as ADEM is of particular relevance to children. ADEM is typically characterized by subacute encephalopathy, often with meningismus and fever, associated with multiple neurological deficits and widespread, asymmetric white matter involvement on MRI. ADEM is classically considered a monophasic demyelinating syndrome, and many paediatricians would not view MS as a possible outcome in these children. However, as was highlighted at the recent Canadian Congress of Neurological Sciences meeting in June 2003, the clinical definition of ADEM is controversial, the outcome is varied, and some children with ADEM do develop MS. Hence, the child neurology community in attendance at the meeting applauded the call for a prospective study of paediatric CIS, and of ADEM in particular.

Methods

The study will collect non-nominal, detailed case-specific data that will document the clinical features, epidemiological characteristics, familial autoimmune profile, and the current medical care practices provided to children with CIS. As noted above, one of the barriers to the diagnosis of paediatric MS may be a lack of diagnostic awareness of MS as a possible outcome of acute CNS demyelination in children. In order to understand current clinical practice, and to explore whether the CPSP influences clinical practice and physician awareness, a one-time survey question asking all CPSP respondents whether they view MS as a possible outcome of acute demyelination was posed prior to the start of the study. Once the CPSP study on acute demyelinating syndromes of the CNS is initiated, information will be collected on the detailed questionnaire to indicate whether the reporting physician discussed with families the potential for the future diagnosis of MS. A follow-up survey at the completion of the surveillance period will again query CPSP respondents as to whether they consider MS a possible outcome of CNS demyelination.

The individual and societal impact of CNS demyelination in childhood requires appreciation of the number of affected children, their immediate clinical recovery and residual sequelae, including the medical care practices associated with this, and the risk of conversion to the chronic disease, MS. The CPSP surveillance project will directly enhance care of affected children by increasing diagnostic awareness of treating physicians, and by facilitating contact between paediatricians and study investigators who are familiar with the care of children with CIS/MS. Ultimately, barriers to the diagnosis of paediatric MS will be reduced, facilitating prompt and specialized care for children with this disease.

To this end, a website will be created to provide clinicians and families with information on the signs, symptoms, and therapies for CNS demyelination (acute demyelination and MS). The web page will also list ongoing research, for which children with CNS demyelination may be eligible. Paediatric health-care providers who identify cases will also be contacted to alert them to research options, which

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can then be offered to the families at the discretion of the treating physician. Referral of eligible patients for research studies will occur independent of the CPSP, and under no circumstances will pressure be applied to CPSP respondents to enlist patients for research unless this is viewed by the respondent as being in the best interests of the child and family.

Objectives

1. To increase awareness and understanding of paediatric CIS and MS among Canadian paediatricians.
2. To define the incidence of the various forms of paediatric CIS in Canadian children.
3. To evaluate the epidemiological features and familial autoimmune profile of children with CIS.
4. To describe current treatments offered to children with CIS across Canada, with attention to differences in treatment protocols across regions and between community and tertiary care facilities.
5. To evaluate paediatric and paediatric neurologist practices in discussing with families the possibility of MS following CIS in childhood.

Case definition

Report any child less than 18 years of age with one of the following syndromes:

- Acute loss of vision (**optic neuritis**): decreased visual acuity of one or both eyes, typically maximal over a period of days, often associated with pain. CT/MRI may show swelling and abnormal signal of optic nerves.
- Spinal cord dysfunction (**transverse myelitis**): weakness and/or numbness of both legs +/– arms, often associated with bladder retention with maximal deficits 4 to 21 days after symptom onset. MRI may demonstrate swelling and/or abnormal signal in the spinal cord.
- Acute neurological deficits: **acute neurological dysfunction** (i.e., weakness, numbness/tingling, loss of balance, impaired eye movements, double vision, poor coordination) maximal within 4 to 21 days after onset associated with MRI evidence of at least one area of abnormal white matter signal of the brain or spinal cord. Level of consciousness should be normal, and fever or neck stiffness absent.
- Acute disseminated encephalomyelitis (**ADEM**): acute neurological deficits (weakness, numbness, loss of balance) associated with at least two of the following: (1) viral prodromal illness within the last 28 days; (2) fever, (3) stiff neck, (4) headache, (5) altered level of consciousness or behavior, or (6) seizures. MRI shows multiple areas of abnormal signal in the white matter.

Exclusion criteria

- Demyelination of the peripheral nervous system (i.e., Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy)
- Leukodystrophies (i.e., metachromatic leukodystrophy, adrenoleukodystrophy, etc.) or mitochondrial disease
- Active CNS infection (i.e., bacterial meningitis, herpes simplex encephalitis, Lyme disease, HIV, HTLV-1, West Nile virus)
- Radiation/chemotherapy associated white matter damage

Duration

April 2004 to March 2007

Expected number of cases

Review of hospital ICD-10 data from 12 paediatric facilities indicates that approximately 100 children are diagnosed with CIS every year. The number of children with milder symptoms, who are cared for by community paediatricians, is unknown. Surveys of adult MS clinics in Canada demonstrate that approximately 5% of all MS patients have the onset of symptoms prior to the age of 16 years.[1,2] Based on an annual incidence of 1,100 adult MS cases per year in Canada (MS Society of Canada), approximately 55 children should meet the diagnostic criteria for MS each year. It is anticipated that as many as 100 children with CIS, and 55 children with established MS will be confirmed by the CPSP project per year. The study will run for three years, as enrolment in the first year may be limited until awareness of the study is maximized.

Ethical approval

The Hospital for Sick Children

Analysis and publication

It is anticipated that abstracts will be produced as early as the end of the first year, and submission for publication of the clinical-epidemiological features of paediatric CIS will be completed at the end of the third year of surveillance.

References

1. Boiko A, Vorobeychik G, Paty D, Devonshire V, Sadovnick D. Early onset multiple sclerosis: A longitudinal study. *Neurology* 2002; 59(7):1006-10.
2. Duquette P, Murray TJ, Pleines J, Ebers GC, Sadovnick D, Weldon P et al. Multiple sclerosis in childhood: Clinical profile in 125 patients. *J Pediatr* 1987; 111(3):359-63.