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Original Article

Nationwide Incidence of Acquired Central Nervous System Demyelination in Icelandic Children

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ABSTRACT

INTRODUCTION: Recognizing acquired demyelinating syndromes and multiple sclerosis is important to commence early treatment. The objective of this study was to describe the incidence of acquired demyelinating syndromes and multiple sclerosis among the entire Icelandic pediatric population according to recently promoted criteria. **PATIENTS AND METHODS:** The study included all children in Iceland (<18 years) with acquired demyelinating syndromes and multiple sclerosis from 1990 to 2009 with a minimum of 5-year follow-up. Clinical data were gathered and radiological images reviewed. The cohort included all patients with acquired demyelinating syndromes and multiple sclerosis in the Icelandic pediatric population. **RESULTS:** Eighteen patients with acquired demyelinating syndromes and multiple sclerosis were included, the total annual incidence being 1.15/100,000 (acquired demyelinating syndromes 1.02 and multiple sclerosis 0.45/100,000). The median age at diagnosis was 14.25 years (range 1.25-17.5 years). Thirteen patients were initially diagnosed with clinically isolated syndrome, two had acute disseminated encephalomyelitis, two had multiple sclerosis, and one had neuromyelitis optica. Seven children were diagnosed with multiple sclerosis; three patients with clinically isolated syndrome developed multiple sclerosis after the age of 18 and were not included in the multiple sclerosis group. The gender ratio was equal. Of the nine girls, seven were diagnosed with clinically isolated syndrome. Most patients (11 of 18) were diagnosed during the period January through March. Oligoclonal bands in cerebrospinal fluid were exclusively found in patients with multiple sclerosis and clinically isolated syndrome and 13 of 14 available magnetic resonance images revealed clear abnormalities. **CONCLUSION:** The annual incidence of acquired demyelinating syndromes and multiple sclerosis in Iceland was 1.15/100,000 children. The risk of progression from clinically isolated syndrome to multiple sclerosis was high. There was no female preponderance.

Keywords: acquired demyelinating syndrome, children, multiple sclerosis, ADEM, CIS, transverse myelitis

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Introduction

Multiple sclerosis (MS) is uncommon in children and less than 10% of patients with MS are diagnosed during childhood. A diagnosis of MS before age 10 years is very rare.[1-7] The cause of this neurodegenerative disorder is unknown, but environmental factors are believed to affect genetically susceptible individuals and increase the likelihood of developing MS. Relapsing-remitting MS (RRMS) is the most common form, and the majority of those diagnosed in childhood have RRMS.[8,9] Some patients diagnosed with RRMS develop secondary progression later in life. It seems that the younger the patient is at diagnosis, the slower the disease progresses.[9]

Acquired demyelinating syndromes (ADS) presenting as a single demyelinating attack can herald the onset of the chronic MS disorder consisting of recurrent demyelinating attacks in different places within the central

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nervous system (CNS). The International Pediatric Multiple Sclerosis Study Group (IPMSSG) published consensus definitions of pediatric CNS ADS and MS in the year 2007 facilitating further research and comparison between studies. These criteria were revised in the year 2012.[10] These definitions categorize ADS into acute disseminated encephalomyelitis (ADEM), clinically isolated syndrome (CIS) (including optic neuritis and transverse myelitis), and neuromyelitis optica (NMO). Patients diagnosed with CIS, often female adolescents, are considered at greater risk of progressing to MS than children diagnosed with ADEM.[2,10-13] NMO is an extremely rare disease in children.

Although medical history and thorough physical examination provide the basis for the diagnosis of ADS and MS, cerebrospinal fluid (CSF) analysis and magnetic resonance imaging (MRI) provide important diagnostic aid. Oligoclonal bands in the CSF are frequently encountered in patients with CIS and MS but are not as common among patients with ADEM.[10,11,14-17]

Treatment, often consisting of high-dose corticosteroids, aims to reduce inflammation in the CNS during acute attack. Immunomodulating drugs reduce the relapse rates and slow down the disease progress.[9,18] Because of the rarity of these diseases in the pediatric population, the efficacy of immunomodulating drugs is not as well documented as in the adult population.[18,19] Supportive treatment also plays an important role.

The purpose of this study was to establish the nationwide incidence of ADS and MS in the entire pediatric population of Iceland. With a total population just over 300,000 in Iceland, the number of cases is small but all cases of pediatric ADS and MS are diagnosed and managed by pediatric neurologists at The Children's Hospital Iceland.

Patients and Methods

A retrospective, nationwide survey was done of all children, age 0-18 years, in Iceland diagnosed with ADS and MS during a 20-year period, 1990-2009. The diagnosis included ADS (ADEM, CIS, and NMO) and MS. Patients were followed up for at least 5 years to evaluate further progress to MS after the initial attack. In addition to the diagnosis in the medical records, the patients had to fulfill the diagnostic criteria made by the IPMSSG.[1,10]

All patients were diagnosed and treated by one of the three pediatric neurologists at The Children's Hospital Iceland, and available MRIs during first demyelinating attack were reviewed by one of the authors (HE), an experienced radiologist. All diagnoses were reviewed by one of the authors (ÓT), an experienced pediatric neurologist.

The following information was recorded from the medical records: age at diagnosis, year and date of diagnosis, gender, family history, history of recent infections before diagnosis, associated diseases or chronic illnesses, clinical symptoms at diagnosis, disabilities, recurrent attacks, and treatment. Results of blood tests (full blood count, viral antibodies, NMO antibodies) and CSF (number and differentiation of leukocytes, proteins, and oligoclonal bands) tests were collected from hospital records.

When reviewing MRI, special attention was given to the number of white matter lesions in the brain, lesions perpendicular to the corpus callosum, number of periventricular lesions, subcortical lesions, lesions in the corpus callosum, cerebellar lesions, black holes, diffuse lesions, spinal cord lesions, and contrast enhancement in the brain and spinal cord.

Maximal disability due to the first demyelinating attack was determined using the Expanded Disability Status Scale (EDSS) and compared with the EDSS score on last visit to a pediatric neurologist or to an adult neurologist for those older than 18 years at last follow-up.

When evaluating the age at diagnosis, the patients were assigned to one of six 3-year periods. Age-specific incidence was calculated using Icelandic population statistic for children younger than 18 years (www.statice.is). When calculating seasonal variation at the time of diagnosis, the year was divided into four periods, January to March, April to June, July to September, and October to December.

For statistical calculation (Poisson regression), SPSS (17.0) was used and statistical significance set at $P < 0.05$.

The study was approved by The National Bioethics Committee, The Data Protection Authority, and the relevant hospital managers.

Results

Eighteen patients who fulfilled the IPMSSG criteria were included in the study, nine boys and nine girls. The annual incidence of all demyelinating diseases, including ADS and MS, in Icelandic children younger than 18 years was 1.15/100,000 children per year. The median age at diagnosis was 14.25 years (range, 1.25-17.5 years). The annual incidence of ADS only was 1.02/100,000 children. Within the ADS group, 13 patients (72%) had CIS (incidence, 0.83/100,000 children), two patients (11%) had ADEM (incidence, 0.13/100,000), and a single patient (5.5%) had NMO (incidence 0.06/100,000). Two patients (11%) were diagnosed with MS at presentation due to previous history and older lesions on MRI. Five additional patients, initially diagnosed as having CIS, progressed to MS within the study period before reaching age 18 years. The incidence of pediatric MS was 0.45/100,000.

Three additional patients belonging to the CIS group were diagnosed with MS after reaching age 18 years and were not included in our incidence calculations of MS. Of those diagnosed with MS (including those diagnosed after age 18 years), five patients were males and five females.

At the patients' last visit to a neurologist, eight patients with MS had the RRMS form. Data were not available for two patients.

The number of patients diagnosed per year was similar except for the year 2009 when five children were diagnosed with ADS and MS. This difference is statistically significant ($P < 0.05$). In 2009, two patients were diagnosed with CIS, two with MS, and one patient was diagnosed with NMO.

Three patients were diagnosed before age 12 years, one patient had ADEM and the other two were diagnosed with CIS (Fig 1).

Of the nine girls, seven were diagnosed with CIS, one was diagnosed with ADEM, and one with MS at first presentation. Six of the nine boys were diagnosed with CIS, one was diagnosed with MS, and one with ADEM. The only patient with NMO was a 15-year-old boy. The gender ratio was 1:1 (Fig 2).

Eleven (61%) of the patients were diagnosed during the period January through March.

Information about recent infections was often inconclusive. Medical history often indicated recent infections, and serum antibodies were measured in 11 patients, seven of those had increased antibodies indicating recent infections. Of the seven patients, three patients had increased antibodies against mycoplasma and two against herpes simplex virus I. Antibodies against adenovirus and respiratory syncytial virus were increased in one patient each. Most