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Original article

The natural course of clinically isolated syndrome in pediatric patients

Cha Gon Lee [a], Bolyun Lee [b], Jeehun Lee [c], Munhyang Lee [c,*]

[a] Department of Pediatrics, Eulji General Hospital, College of Medicine, Eulji University, Seoul, Republic of Korea
[b] Department of Pediatrics, Pusan Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea
[c] Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

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Abstract

Background: The first episode of central nervous system (CNS) symptoms with a presumed inflammatory demyelinating cause is defined as clinically isolated syndrome (CIS) according to the 2007 consensus of the International Pediatric Multiple Sclerosis Study Group, which developed diagnostic criteria for CNS demyelination disease in children. Using this definition of CIS, we attempted to identify the natural course of pediatric patients with CIS in a single Korean institution and to determine the factors affecting their prognosis. *Methods:* We retrospectively reviewed the medical records of all pediatric patients (age <18 years old) who presented with clinical symptoms of CNS events between 1997 and 2008. *Results:* We identified 32 patients with CIS. Their mean age with standard deviation was 10.0 ± 4.1 years. The most common type of presentation of CIS was optic neuritis (ON). Sixteen (16/32, 50%) patients experienced a second demyelinating event. The mean interval between the first event and the recurrent episode was 21 ± 20 months. The mean follow-up was 6.1 ± 1.6 years. Eleven (34%) patients developed childhood onset multiple sclerosis (MS). In contrast to previous studies, asymptomatic brain lesions on magnetic resonance imaging (MRI) and the presence of cerebrospinal fluid (CSF) oligoclonal bands (OCBs) were not predictors of conversion to MS. *Conclusion:* In our study, a second relapse and initial presentation with brain stem, cerebellar, cerebral dysfunction, or multifocal CIS were strongly associated with the development of MS ($p = 0.002$). Despite clinical definitions and increased understanding of CIS in children, challenges remain in predicting its progression to a chronic demyelinating disease.

Keywords: Demyelinating disease; Child; Multiple sclerosis; Neuromyelitis optica; Autoimmune disease

1. Introduction

Acquired noninfectious inflammatory demyelinating disorders of the central nervous system (CNS) display various clinical spectrums, ranging from a self-limited course to chronic relapsing-remitting disease. In 2007, the International Pediatric Multiple Sclerosis (MS) Study Group arrived at a consensus on diagnostic criteria for CNS demyelination disease in children [1]. According to its criteria, the initial clinical demyelinating event can be acute disseminated encephalomyelitis (ADEM), neuromyelitis optica (NMO), or clinically isolated syndrome (CIS). Clinical features of ADEM must include signs of encephalopathy, such as behavioral changes, or alteration in consciousness. The definition

* Corresponding author. Address: Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul, Republic of Korea. Tel.: +82 2 3410 3539; fax: +82 2 3410 0043.
E-mail address: mhlee091@skku.edu (M. Lee).

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of NMO depends on the presence of sequential or concomitant optic neuritis (ON) and acute myelitis. Diagnostic criteria for NMO are a spinal magnetic resonance imaging (MRI) extending over three or more segments or NMO-IgG (aquaporin 4) positive on antibody test. CIS is defined as a first episode of CNS symptoms with a presumed inflammatory demyelinating cause that does not meet criteria for ADEM and NMO [1]. Many studies investigated the clinical course of CNS demyelinating disorders prior to the development of the consensus on diagnostic criteria [1]. However, the lack of a clear definition of pediatric CIS made it difficult to compare the diagnosis, treatment, and prognosis of this disease [2]. Since the 2007 consensus, several studies of patients with CIS have aimed to determine risk factors for MS and appropriate treatment options [3]. Despite those studies, the management of pediatric CIS, especially maintenance therapy aimed at preventing recurrence, remains controversial [4]. More research is needed to understand the prognosis of pediatric CIS. In this study, using the recent consensus definition of CIS, we attempted to identify the natural course of pediatric patients with CIS in a single Korean institution and to determine the factors affecting their prognosis.

2. Patients and methods

We retrospectively reviewed the medical records of all patients (age <18 years old) who presented with clinical symptoms of CNS demyelinating disease. All the patients were enrolled at Samsung Medical Center, a tertiary care university hospital, between August 1997 and August 2008. This study included patients whose clinical courses were followed up for at least 2 years after the first event. Forty patients who experienced an initial clinical CNS demyelinating event were identified. The 2007 consensus definition [1] was used to reclassify the cases into CNS disorders. CIS was detected in 32 patients, ADEM in seven patients, and NMO in one patient. We excluded eight patients with ADEM and NMO. We analyzed the sex, age, clinical features, laboratory results, neuroimaging findings, and management of the 32 patients with CIS. Based on clinical neurological symptoms and compatible CNS lesions on brain MRI, CIS was subclassified into five groups: unilateral or bilateral ON, transverse myelitis, brain stem or cerebellar dysfunction, cerebral dysfunction, and multifocal CNS dysfunction. Isolated ON was characterized as symptoms indicating the involvement of the visual pathway and confirmation by an ophthalmologist or MRI. Acute onset symptoms of sensory, motor, or autonomic dysfunction attributable to the spinal cord were categorized as transverse myelitis. Diplopia, dysarthria, ataxia, ocular dysmetria, and facial weakness were sorted according to brain stem or cerebellar dysfunction. Hemiplegia, hemiparesis, and involuntary movements were recorded as cerebral dysfunction. Any neurological presentation affecting the optic pathway, spinal cord, brain stem, cerebellum, or cerebrum was classified as multifocal dysfunction.

To identify predictors of a second event, statistical analysis was performed with Fisher's exact test and Welch's two sample t-test using SPSS Statistics version 18 (IBM corporation, NY, US). We considered $p < 0.05$ as statistically significant.

Ethical approval for this retrospective study was provided by the institutional review board of Samsung Medical Center in Seoul, Korea (SMC 2012-02-082-001).

3. Results

We identified 32 patients (20 females, 12 males) who fulfilled the inclusion criteria for CIS. Their mean age with standard deviation was 10.0 ± 4.1 (range, 1.5–16.9) years. The most common type of presentation of CIS was ON ($n = 14$; unilateral 9, bilateral 5), as shown in Fig. 1. Sixteen (16/32, 50%) patients experienced a second demyelinating event. The mean interval from the first event to a recurrent episode was 21 ± 20 (range, 0.8–69) months. In the group of patients with ON, the presence of incidentally identified demyelinating lesions was not statistically related to a second event ($p = 1.000$), as shown in Table 1. The recurrence rate of a second event was higher in the patients with cerebral dysfunction (3/3, 100%), multifocal dysfunction (2/3, 66.7%), and brain stem or cerebellar dysfunction (3/5, 60%) than in those with ON (6/14, 42.9%) and transverse myelitis (2/7, 28.6%). However, there was no statistically significant differences ($p = 0.489$) between the five groups when CIS was classified according to clinical neurological symptoms and compatible CNS lesions on brain MRI, as shown in Table 1.

The mean follow-up was 6.1 ± 3.1 (range, 2.4–12.9) years. Fig. 1 shows the final diagnosis during the follow-up period. Sixteen (50%) patients were diagnosed with CIS without a recurrent episode. The mean follow-up time of the 16 patients without a recurrent episode was 5.4 ± 3.1 (range, 2.5–12.9) years. The final diagnosis of each of the 16 patients in the five subgroups with a recurrent episode was as follows; the group of six patients with ON were finally diagnosed by MS ($n = 2$), recurrent ON ($n = 2$), Sjögren disease with systemic lupus erythematosus (SLE) ($n = 1$), and relapsing NMO ($n = 1$); the group of two patients with ATM were finally diagnosed by recurrent ATM ($n = 1$) and MS ($n = 1$); the group of patients with brain stem/cerebellar dysfunction ($n = 3$), cerebral dysfunction ($n = 3$), and multifocal dysfunction ($n = 2$) who experienced a second episode were finally diagnosed with MS. Eleven (25%; 8 females, 3 males) patients developed childhood-onset