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□ Case Report □

A case of childhood relapsing/remitting multiple sclerosis and interferon β-1b treatment in a Korean patient

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Multiple sclerosis (MS) is a demyelinating disorder that affects discrete areas of the CNS, including the optic nerves, in a quite variable relapsing-remitting fashion over a prolonged period of time. Although MS is usually considered to be a disease that affects peoples in early to middle adulthood, children do develop multiple sclerosis. The frequency of MS onset before the age of 15 years is 2.7-5% of all cases, while MS onset during infancy and early childhood was observed to be 0.2-0.7% of all cases. We report here on a Korean case of a relapsing-remitting MS female child who was treated with four rounds of intravenous methylpredinsolone pulse therapy and preventive Interferon-β-1b (Betaferon®). **(Korean J Pediatr 2007;50:580-584)**

Key Words : Multiple Sclerosis, Optic neuritis, Interferon-β-1b (Betaferon®)

Introduction

Multiple sclerosis (MS) is a demyelinating disorder that affects discrete areas of the CNS, including the optic nerves, in a quite variable relapsing-remitting fashion over a prolonged period of time. Although usually considered to be a disease that affects peoples in early to middle adulthood, children do develop multiple sclerosis[1].

The estimated average world prevalence of MS is about 50 persons per 100,000 and the frequency of MS onset before the age of 15 years is 2.75% of all cases, while MS onset during infancy and early childhood was observed in 0.2-0.7% of all cases[2]. MS patients are generally treated with corticosteroids and severe cases may benefit from plasma exchanges. The approved disease-modifying therapies are interferon-β-1b, glatiramer acetate and mitoxantrone[1].

We report here on a Korean case of a relapsing-remitting MS female child who was treated with four rounds of intravenous methylpredinsolone pulse therapy and preventive interferon-β-1b (Betaferon®).

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Case Report

A 10 year old girl was born by normal vaginal delivery at 40 weeks; she had a birth weight of 3,200 gm. She experienced febrile seizure for the first time at 6 years of age and was admitted 3 months later due to her first attack of acute left side hemiparesis. At the time, the brain MRI imagings showed multifocal nodular and patch infiltrations in the white matter (Fig. 1A, 1B) suggesting an episode of acute disseminated encephalomyelitis (ADEM). Injections of intravenous methylprednisolone (30 mg/kg/day) were given for 5 days and this was tapered down with using oral doses over 7 weeks; this resulted in complete recovery. The laboratory results at the time showed nothing specific on the CBC, and the CSF study was normal with negative results for the CSF adenovirus DNA probe, the CSF Herpes Simplex virus PCR, CSF Varicella Zoster virus PCR, the oligoclonal IgG assay and the enterovirus culture, except that the CSF myelin basic protein (MBP) was increased to >8 ng/mL. The serum arylsulfatase A and Japanese encephalitis virus antibody tests were negative. 2 months after discharge, she arrived to the ER with left side clonic type status epilepticus, and so oxcarbamazepine (Trileptal® 30 mg/kg/day), was administered,

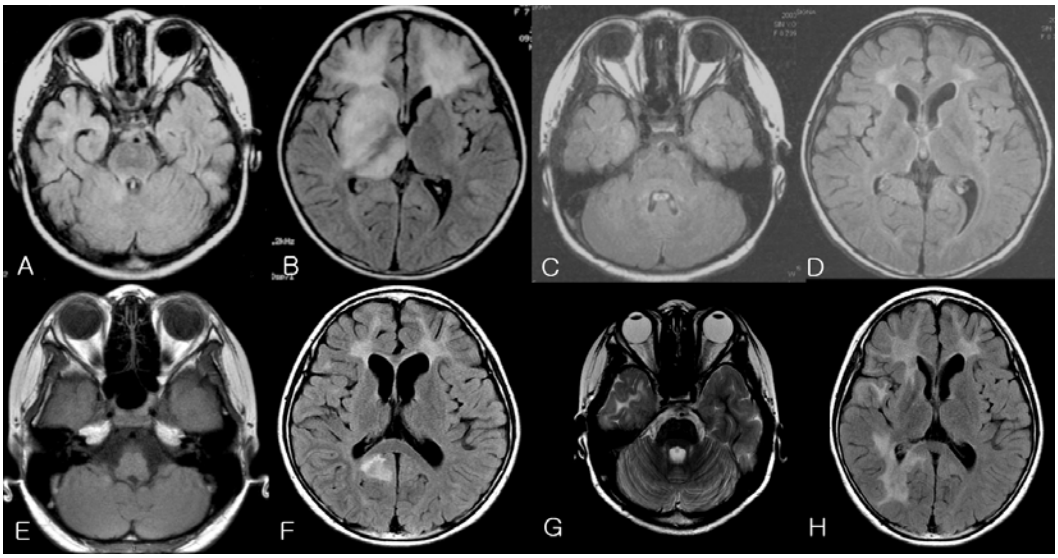

Fig. 1. The brain MRI showed multifocal nodular and patchy infiltrations with meningeal enhancement in both frontal lobes and the right basal ganglia area at the 1st attack (A, B). The brain MRI 6 months later after the 2nd attack showed improvement except for both frontal lobes (C, D), and the brain MRI after the 3rd attack 38 month later showed optic nerve atrophy and new right occipital area lesion (E, F). The 4th attack showed left optic nerve swelling and patch infiltration on both the frontal and right parieto-occipital lobes 40 month later (G, H).

which is an anticonvulsant. After recovering relatively well, she was admitted again 6 months after the first attack with complaints of headache and left periorbital pain, and the brain MRI imaging showed improvement except for both frontal lobes (Fig. 1C, 1D), and optic nerve atrophy was seen on fundoscopy (Fig. 2A, 2B). The EEG showed high amplitude 2 to 3 Hz delta activities on the anterior head region and spike discharges from the right and left frontal areas. Her psychological assessment seemed low normal with scores of the Full scale IQ (FIQ)=84, the verbal IQ (VIQ)=92 and the performance IQ (PIQ)=79, as measured by the Korean Wechsler Intelligence scale for Children (K-WISC), except for the MQ of 65 according to the Rey-Kim memory exam that showed her memory was retarded compared to that of her intelligence. The laboratory results showed nothing specific on the CBC, and the CSF study was normal include IgG index [(serum albumin ÷ serum IgG)÷(CSF albumin÷CSF IgG)] was 0.589 (normal<0.7) and except that CSF MBP was increased to 4.38 ng/mL (normal<4.0). She was then diagnosed with MS and she went under a second round of methylprednisolone pulse therapy (30 mg/kg/day) for 5 days; this was followed by tapering down the oral doses over 7 weeks. Her seizure continued after that, so oxcarbamazepine with topiramate (2.5 mg/kg/day) were added to the medication and then she did well for a year and 8 months. But 38 months after the first attack, she was again admitted with a third attack of headache and left side tonic-clonic seizure; Fig. 1. E, F show the brain MRI at the time. Her symptoms improved after methylprednisolone pulse therapy for 3 days and tapering down the oral dose over 3 months. 2 months later, she was readmitted with a 4th attack of left visual impairment and the brain MRI taken at that time is seen in Fig. 1G, 1H. She received the diagnosis of relapsing-remitting MS. Interferon-β-1b (Betaferon®, SheringAG, Germany) at 5 million units was injected subcutaneously every other day for disease-modifying therapy. She suffered side effects of back pain and myalgia for 2 days, but she has been well for the past 14 months with no further side effects. She is now under outpatient follow-up.

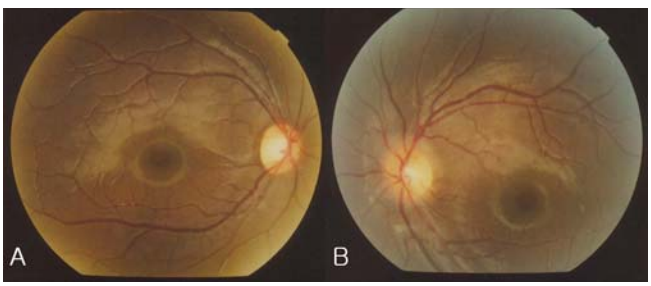

Fig. 2. A, B) Fundoscopy showed the optic nerve atrophy at the 2nd attack.

Discussion

Although MS is primary a disease of early and middle adulthood, children can develop MS. The estimated average world prevalence of MS is about 50:100,000 and the frequency of MS onset before the age of 15 years is 2.7 to 5% of all cases, while an onset during infancy and early childhood has been observed in 0.2 to 0.7% of all cases[2, 3].

The definite cause for MS has not yet been determined, but it is considered to be the result of genetic and environmental factors. Its been reported to be related to the class II MHC alleles DR 15, DQ 6 and DR2; 15% of MS patients have MS relatives, and the siblings of MS patients especially show the highest risk[4]. As for the non genetic factors, infection, trauma, pregnancy etc are known to be the promoting factors.

MS lesions are similar to that of ADEM, which is an autoimmune disease that takes the form of latent hypersensitive reaction, and antibody to MBP has been found in the plasma and CSF of MS patients. Such antibodies react to MBP and other myelin lipoprotiens in the CSF of the majority of MS patients and so this proves MSs relation to humoral immunity[5]. The pathologic characteristics are a loss of myelin without atrophy of neurons and axons. In the early lesions, inflammatory reactions due to lymphocytes and plasma cells surrounding the vessels are seen together with the destroyed myelin tissue; this is followed by lipid metabolic products of the myelin forming plaques a few months later on, and clear demyelination together with the loss of oligodendrocytic cells can be observed[5, 6].

The symptoms vary depending on the sites or the period of affliction, but the first symptoms usually include muscle weakness, a tingling sensation in one or more limbs, visual disturbances, diplopia, paresthesia etc, and the limb weakness is progressive. As the cerebellum becomes affected, disturbance in walking, ataxia, dysarthria, tremor and motor discordance are seen. In 25% of MS cases, the first manifestation occurs in the form of optic neuritis, and this is more common in children. Partial or complete loss of vision of one eye progresses rapidly over hours to days, and this can occur in both eyes. Diplopia and visual disturbance may occur as well. In the cases with cord lesion, control of the bladder and intestine can be impaired. In childhood MS, encephalitis symptoms like headache, nausea, vomiting, fever, seizure, loss of consciousness and dysfunction of the cerebellum of the brainstem can occur[7].

According to the diagnostic criteria by Rose in 1976, relapse and remission that are repeated more than twice with a recent one month gap in between with a slowly progressive course, and more than one lesion in the white matter of the brain or the cord that causes neurologic symptoms, must be detected to arrive at a diagnosis of MS[7]. Because it is not possible to diagnose MS with using this criteria at its first occurrence, Poster et al in 1983 added a lab test that enables the first symptoms to lead to the diagnosis[8]. McDonald in 2000 added extra clinical symptoms, the MRI imaging and CSF analysis to the diagnosis criteria. CSF exams generally show an increased total IgG concentration and the detection of an oligoclonal IgG band on immune-electrophoresis. Multifocal enhanced density lesions in the white matter together with plaques in the brainstem, cerebellum and cord can be seen on the T2 imagings of MRI[9, 10]. An international consensus proposed four subgroups of multiple sclerosis. 1) Relapsing-remitting MS: clearly defined disease relapses with full recovery or with sequelae and residual deficit upon recovery. 2) Secondary progressive MS: an initial relapsing-remitting course is followed by progression. 3) Primary progressive MS: disease is progressive from the onset with only temporary plateaus and minor improvements allowed. 4) Progressive-relapsing MS: Progressive disease from the onset with clear acute relapses[1].

ADEM, Lyme disease, progressive multifocal leukoencephalopathy, HIV associated myelopathy and HTLV-1 etc must be differentiated from MS, and ADEM is very difficult to distinguish from MS according to the symptoms and CSF results, which also show white matter lesion on MRI. The MRI follow up exams of MS patients every few months reveal that the high density of lesion at the first occurrence are decreased, but there are new lesions with enhanced density and they are detectable upon injection of gadolinium DTPA contrast. This can reveal lesions at different stages of activity, and this enables MS to be distinguished from ADEM, which show lesions during the same period[11, 12].

Treatment of MS includes therapy for the of acute exacerbations and also disease-modifying therapy. Acute exacerbations of MS are generally treated with a short course of oral corticosteroid, intravenous methylprednisolone and plasma exchanges. The approved disease-modifying therapies are interferon-β-1b (Betaseron or Betaferon), glatiramer acetate (Copaxone,copolymer-1) and mitoxantrone [No-

vantrone(Serona, Inc, Rockland,MA)].

Interferon-β-1b (Betaseron or Betaferon) became the first medication approved by the U.S Food and Drug Administration for the treatment of relapsing-remitting MS and it showed a 31% reduction in the exacerbation rate compared with placebo in 1993[1]. Administration of all interferon-β products requires frequent parenteral injections, either subcutaneous or intramuscular. As for the side effects, injection site redness, pain necrosis, flulike symptoms (fever, myalgia, chills), depression, anxiety, confusion, leukopenia and hepatotoxicity can be seen[15-17].

The prognosis of MS is usually poor and only 5-10% of patients have a mild course. Childhood MS patients, in comparison to adults, usually relapse within a year (40-60%) but the long term prognosis at 8 to 10 years is less severe with only 15-20% showing severe impairment. Our case had 4 attacks with symptoms such as hemiparesis, seizure, headache and periorbital pain accompanied by optic neuritis. The brain MRI imagings showed lesions that matched those of MS, and she fully recovered with methylprednisolone pulse therapy after every attack. According to the new sequelae on brain MRI, her disease was consiered to be relapse-remitting type, but if there are any signs of progression in the future, then the possibility of secondary progressive MS can not be ruled out. Since the period after interferon-β-1b treatment is only 17 months, further observation is necessary.

한 글 요 약

소아 재발/완화형 다발성 경화증 환자에서 인터페론 베타 1b 치료 1례

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다발성 경화증은 중추신경계 백질의 여러 부위를 시간 간격을 두고 침범하는 만성재발성 질환이다. 주로 20세에서 40세 사이에 발병하며 15세 이하 소아에서도 3-5% 정도 발병하는 소아기에는 매우 드문 질환이다. 원인은 아직 정확히 밝혀지지 않았으나 유전적, 환경적 및 감염과 연관된 자가면역반응 등 여러요인이 복합적으로 작용하는 것으로 생각하고 있다. 임상증상은 침범된 백질 부위에 따라 다양한데 사지근력 약화나 저림, 시력장애, 감각장애, 운동실조 등 다양한 증세로 호전과 재발을 반복한다. 본 저자들은 경련, 왼쪽 편마비 등의 증상으로 6세에 첫 발병 후 메틸프레드니솔론(methylprednisolon) 치료 후 증상 완전 회복 있었으나 6개월 후 경련, 두통, 왼쪽 안와주위 통증 등으로 다시 입원하는 등 4년간 추적 관찰 중 4차례 메틸프레드니솔론 치료 실시하였으나 다른 양상의 신경학적 증상으로 재발하여 Interferon-β-1b(Betaferon®, SheringAG, Germany) 예방 치료를 실시한 다발성 경화증 환자 1례를 경험 하였기에 문헌 고찰과 함께 보고하는 바이다.

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