Subacute sclerosing panencephalitis (SSPE) associated with congenital measles infection

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SUMMARY: Şimşek E, Öztürk A, Yavuz C, Kocabay K. Subacute sclerosing panencephalitis (SSPE) associated with congenital measles infection. Turk J Pediatr 2005; 47: 58-62.

A 13-month-old male presented with repetitive episodes of myoclonic jerks of the head and extremities for two months. His past medical history revealed that his non-immunized mother had measles at the time of delivery. Measles antibody titers in serum and cerebrospinal fluid (CSF) were 1/512 (hemagglutinin inhibition [HI]) and 1/128 HI, respectively.

Immunofixation electrophoresis of CSF revealed an oligoclonal IgG band. The magnetic resonance imaging (MRI) of the brain on T2-weighted images showed lesions of high signal intensity in the subcortical white matter. Electroencephalography (EEG) revealed periodic high-amplitude slow waves. Diagnosis of subacute sclerosing panencephalitis (SSPE) was based upon clinical presentation, a characteristic EEG, and abnormal CSF studies. MRI findings supported the diagnosis. To the best of our knowledge, this is only the 3rd case to date, of SSPE-associated congenital measles in the literature.

Key words: subacute sclerosing panencephalitis (SSPE), congenital measles.

Subacute sclerosing panencephalitis (SSPE) is a postinfectious progressive neurological complication of measles virus infection. Although there are cases reported as young as four months and as old as 52 years, the first clinical symptoms and signs attributable to SSPE are usually observed in children and young adults 6 to 15 years of age after acute measles infection[1,2]. Over half of the cases of SSPE have had a natural measles infection in their first two years of life[3]. It is believed to be the result of persistence of the measles antigen in the central nervous system. Dignosis of SSPE is based upon clinical presentation, a characteristic electroencephalography (EEG), and abnormal cerebrospinal fluid (CSF) studies. No proven effective treatment is currently available, although several therapeutic trials (intravenous gamma globulin [IVIG], plasmapheresis, cytarabine, amantadine, ribavirin, alpha and beta interferon, and Isoprinosine) are underway. Vaccination against measles is still the only effective means of prevention of measles and SSPE. The incidence of SSPE declined dramatically following the introduction of the measles immunization in 1963[4].

We report a case of SSPE-associated congenital measles in a 13-month-old boy who is the 3rd case report in the literature.

Case Report

A 13-month-old male was admitted with repetitive episodes of myoclonic jerks of the head and extremities for two months. His past medical history revealed that he was born by spontaneous delivery at 37 weeks of gestation with a birth weight of 3100 g. Pregnancy was complicated by fever in the last three days before delivery. On the 10th day of life, he had fever (not measured by thermometer), generalized morbiliform exanthema, conjunctivitis, and cough. He was clinically diagnosed by a local pediatrician as having measles infection. He was the first child of his parents, and had received no vaccinations. He had been bottle-fed since birth. His mother informed us that developmentally he was not making good progress. He was not controlling his head, sitting without support, crawling, or vocalizing. He could not differentiate his mother from other people. He had feeding difficulties since the age of six months. Family history was

significant. His mother was febrile for three days before and after delivery. Three days after delivery, she was diagnosed with measles by an obstetrician. The diagnosis was based on generalized morbiliform exanthema, cough, and high-grade fever. After two weeks from delivery date, maternal measles was confirmed by the elevated complement fixation titer of serum measles antibody at the local maternity hospital.

On examination, the patient's weight was below the 3rd percentile, his height was at the 10th percentile, and his head circumference was at the 3rd percentile. He was not sitting, crawling or controlling his head. He had a pulse of 110 per minute. His breathing was irregular and noisy. Moderate hypotonia was observed. Deep tendon reflexes were symmetrically hyperactive. The rest of the clinical examination was unremarkable.

Specific measles antibody titers of serum and CSF were 1:512 hemagglutinin inhibiton (HI) and 1:128 HI, respectively. CSF cell count was 3 lymphocyte/mm^3, protein 25 mg/dl, and glucose 62 mg/dl (simultaneous blood glucose 98 mg/dl). Immunofixation electrophoresis of CSF showed an oligoclonal IgG band (Fig. 1). EEG revealed periodic complexes consisting of bilaterally symmetrical, synchronous, and high-voltage spike and sharp waves (higher than 200 μV) that recurred at intervals of 4 seconds on a slow background (Fig. 2). Magnetic

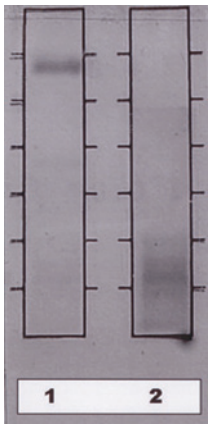

Fig. 1. Cerebrospinal fluid (CSF) immunofixation electrophoresis shows oligoclonal IgG band. 1, CSF protein electrophoresis; 2, CSF IgG immunofixation electrophoresis.

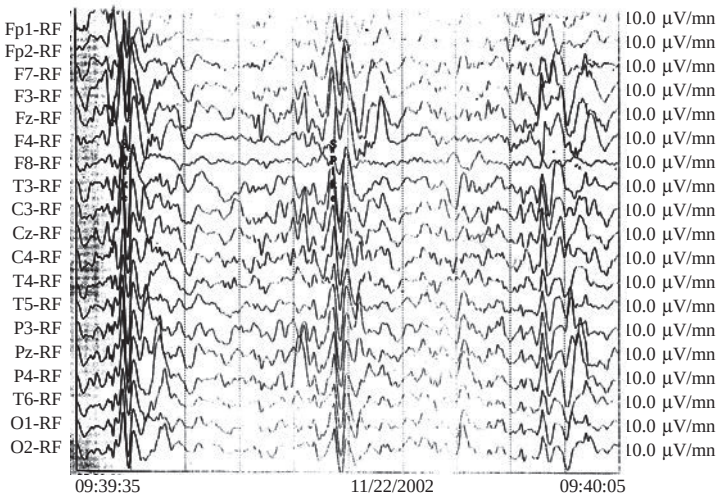

Fig 2. Electroencephalography (EEG) shows periodic complexes consisting of bilaterally symmetrical, synchronous, high-voltage (higher than 200 μV) bursts of triphasic stereotypic delta waves.

resonance imaging (MRI) scans showed asymmetric hyperintense signal in the subcortical white matter of the parietal and occipital lobes (Fig. 3).

Diagnosis of SSPE was suggested by the clinical presentation and confirmed by typical CSF and EEG findings. The parents declined to go to the pediatric neurological center in Ankara because of their economical situation. Because we did not have experience or the appropriate conditions for intraventricular treatment, we chose treatment with oral Isoprinosine (100 mg/kg/day) and intrathecal recombinant interferon alpha-2b (IntronA, Schering), which was started at 1 million units twice a week and then increased to 3 million units. Three months later, his ophthalmologic examination revealed bilateral mild optic atrophy.

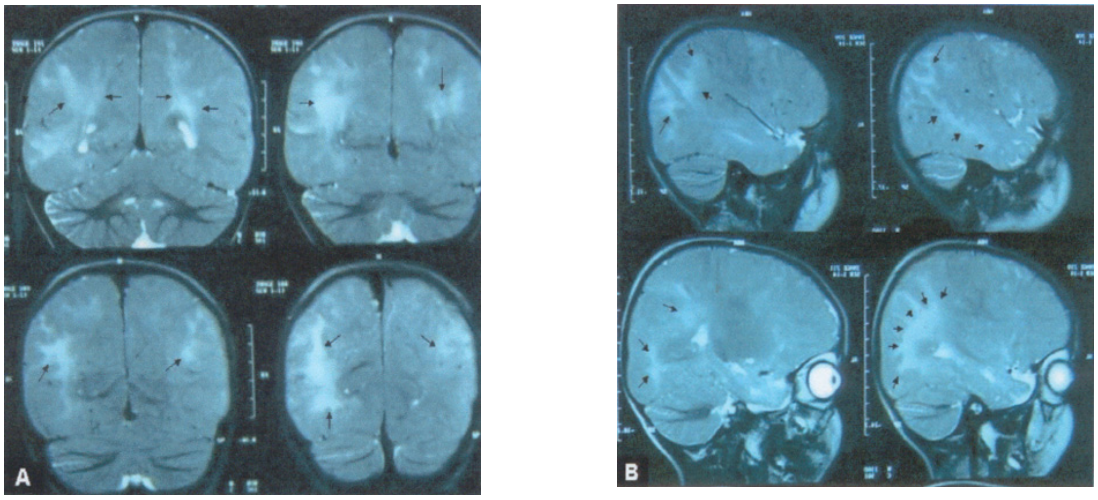

Fig. 3. Magnetic resonance imaging (MRI) scans of the brain at the time of presentation in pediatrics clinic. Coronal T2-weighted images (A) show asymmetric hyperintense signal in the subcortical white matter of the parietal lobes, and sagittal T2-weighted images. (B) show hyperintense signal in the corticosubcortical regions of the occipital lobe (black arrows).

Discussion

The most important risk factor for the development of SSPE in children is measles infection under the age of 15 months[1,5]. Before the vaccination era (<1963), most children were immunized against measles by natural infection and this made acquisition of the virus in the child-bearing ages less likely[6]. Insufficient vaccine coverage in the population decreases the circulation of the virus, but does not eliminate it, increasing the likelihood for a nonimmunized person to be infected in adulthood[6], as seen in the mother of our patient.

Despite a safe, effective, and inexpensive vaccine, measles remains the leading cause of vaccine-preventable childhood mortality. Immunization failure against measles is not only associated with irregular vaccination, but also with the age of vaccination, higher maternal neutralizing measles antibody titers in the infancy period, and lack of the booster dose in the pre-school years[7,8]. The younger mothers who are immunized against measles by natural infection have relatively higher measles antibodies than the older mothers or the mothers who are immunized by vaccination[8]. The overall percentage of young mothers who are immunized against measles by natural infection in Turkey is higher than in developed countries. It can be expected that maternal measles antibody titers in infants in Turkey may be higher than in infants in developed countries. The national immunization course against measles until 1998 in Turkey was implemented by a one-dose vaccine program administered at the age of nine months. Interference by passive (maternal) neutralizing measles antibody has been considered the primary obstacle to the successful immunization of young infants with attenuated measles vaccine[8]. In Turkey, between 15,000-30,000 measles cases have been reported annually since the 1990s[9]. According to the data of the Turkish SSPE Registry Center, from 1975

to 1999, the mean age of measles onset fell from 29 months to 20 months and the mean age of SSPE onset also fell from 13 years to 7.6 years[10]. In contrast, in developed countries, the total incidences of measles and SSPE have declined significantly since the advent of the measles immunization, with the mean age of SSPE onset increasing from <10 years to approximately 14 years[1]. These findings indicate that immunization against measles has still not reached the desired level (nationally 84%)[9]. The World Health Organization (WHO) and the United Nations Children's Emergency Fund (UNICEF) have recommended that , in addition to achieving high coverage with the first dose of measles vaccine, all children should be offered a second opportunity for the measles vaccination to maximize both individual and population immunity[11].

Subacute sclerosing panencephalitis (SSPE) is one of the most important complications of measles in children and young adults. The five diagnostic criteria of SSPE include clinical presentation, a characteristic EEG, abnormal CSF studies, measles antibody in serum and CSF, and brain biopsy. The diagnosis can be reliably established if the patient fulfills three of the five criteria[12]. The initial symptoms of SSPE usually involve regressive changes in intellect and personality. Within several months, neurologic symptoms, most of myoclonic jerks, compound the psychological symptoms. Our patient's clinical course reflected this typical natural history.

Death is usually inevitable within several years of the onset of symptoms[1,3,5].

The Cerebrospinal Fluid (CSF) in SSPE will typically have normal cellular components, glucose and total protein, but markedly elevated values of gammaglobulin and anti-measles antibodies[1,5,12]. CSF's IgG is elevated with oligoclonal bands present by electrophoresis. Typically, serum anti-measles antibody titers are also grossly elevated. The EEG pattern is virtually diagnostic with periodic complexes consisting of bilaterally symmetrical, synchronous, high voltage (200-500 mv) bursts of polyphasic, stereotyped delta waves which repeat at fairly regular 4-10 second intervals and have a 1:1 relationship with myoclonic jerks[1,3,12]. All these characteristic EEG and CSF findings were seen in our case. Brain biopsy is seldom required to establish the diagnosis of SSPE[1,3,5].

Although MRI findings are not essential and specific for the diagnosis of SSPE, it is sensitive in detecting early white matter abnormalities. The MRI profile of SSPE includes focal abnormalities in the subcortical white matter early in the course of disease, as observed in our patient, and diffuse cerebral atrophy at later stages of the disease[13,14]. Cortical and subcortical lesions show some correlation with clinical findings[13], but there is no correlation between the clinical stages MRI findings[13,14].

Although the principal means of preventing measles is the use of live-attenuated measles vaccine, passive immunoprophylaxis can be used to prevent or modify measles if it is given within six days of exposure. Since infants younger than one year, non-immunized pregnant women, and immunocompromised patients (e.g., malnutrition, chemotherapy, and post-transplantation period) are at risk for severe measles infection, they should receive intravenous immunoglobulin (IVIG) following exposure[15]. Non-immunized or immunocompromised patients receiving IVIG at 100 to 400 mg/kg are protected for three weeks from a measles exposure[15]. Unfortunately, we did not have a chance to try IVIG prophylaxis in our case, who was admitted 13 months or more after exposure to measles. If he had been treated with immunoglobulin, the development of SSPE might have been prevented. At this point, one of the treatment protocols for SSPE could have been attempted, although treatment of SSPE remains controversial and no proven effective antiviral therapy is currently available.

According to the data of the prospective studies, which include a reasonable number of cases, the combination of oral isoprinosine and intraventricular interferon has been suggested as the most effective current treatment protocol for SSPE[16-18]. Clinical improvement and remission with these combined treatments were reported in 44% to 59% of cases[18-20]. In contrast, Anlar et al.[19] reported their long-term experience with intraventricular interferon treatment and concluded that the overall prognosis may not be affected whether treated or not. There is no experience for treatment of early onset (<24 months) SSPE associated with congenital measles infection. We found only three reports of SSPE after perinatal infection[20-22]. In one of them, measles infection was symptomatic at the age of four weeks (neonatal measles) and clinical signs of SSPE were observed at the age of 3 years

and 6 months[20]. The other two patients are the only two reported cases of SSPE associated with congenital measles[21-22]. In one patient, the diagnosis of SSPE was made at the age of four months, and he died at the age of 16 months[21]. In the second case, the patient's non-immunized mother had measles at the time of delivery, the diagnosis of SSPE was made at the age of 18 months, and the infant died at the age of 28 months[22]. We report the 3rd case of SSPE associated with congenital measles. These three cases point out that perinatal measles infection shows rapid progress and unfavorable prognosis. In conclusion, there is currently no effective treatment of SSPE. The available options are very expensive and time consuming. The implementation of a two-dose measles vaccination program in the childhood period is the only safe, effective and most inexpensive method to increase population immunity and therefore prevent measles infection and its subsequent complications such as SSPE.

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