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Source / Izvornik: **Collegium Antropologicum, 2006, 30, 959 - 963**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:649032

Coll. Antropol. **30** (2006) 4: 959–963
Case report

Subacute Sclerosing Panencephalitis – The Continuing Threat

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A B S T R A C T

Clinical, epidemiological and laboratory findings of four patients with subacute sclerosing panencephalitis (SSPE), diagnosed in Croatia in 2002, were examined. Patient age at disease onset ranged from 5–11 years. All patients were vaccinated regularly with MMR-vaccine. Two patients had a history of measles infection at the age of six and seven months, respectively. In the other two patients, the disease started immediately after the varicella infection. Complement fixing antibody titre to the measles virus (MV) ranged from 1:1024 to 1:65536 in serum, and from 1:16 to 1:128 in cerebrospinal fluid (CSF). In CSF, no antibodies to varicella-zoster virus were found. Brain tissue samples were obtained at autopsy from two patients. In one patient, electron microscopy demonstrated intranuclear viral inclusions (MV nucleocapsids). MV antigen was detected in brain imprints using IFA in both of them. Viral RNA was found in brain tissue samples only, while plasma, serum and CSF were negative. Nucleotide sequence analysis showed that the viruses detected in brain tissue belong to the wild-type MV D6 genotype[14].

***Key words**: subacute sclerosing panencephalitis, measles, MMR*

Introduction

Subacute sclerosing panencephalitis (SSPE) is a rare, fatal, and late complication of measles. Although SSPE rates reported in the literature vary, it is estimated that approximately one case of SSPE occurs per 10,000 to 1,000,000 reported measles cases[1–3]. The disease occurs 5–10 years after the initial attack of measles. Mental deterioration and myoclonus usually characterize the disease onset, leading to a vegetative, decorticated state, coma and death within 1–3 years. In approximately 10% of cases, there is a fulminant course with death few months after the onset[4]. The exact pathogenic mechanism of SSPE remains unclear. While large amounts of measles antigens are present within inclusion bodies in infected brain cells, no virus particles mature. Viral replication is defective owing to the lack of production of one or more viral gene products, often the matrix protein[5]. It is unknown whether there is a specific predisposing immune defect. A possible risk factor for the development of SSPE is measles infection at an early age, especially before the age of two years[6]. Demonstration of intrathecal measles virus (MV)-specific antibody synthesis or detection of MV-RNA from brain tissue confirms diagnosis[7].

We describe the four SSPE cases diagnosed in Croatia in 2002.

Case Reports

Patient 1

Patient 1 was born in December 1997 in a very high-risk twin pregnancy. She was vaccinated regularly with the measles-mumps-rubella (MMR)-vaccine according to the official immunization schedule[8]. At the age of six months, she was hospitalized for morbilliform rash. In

Received for publication January 11, 2006

August 2002, she developed dysarthria, ataxia and myoclonal jerks. The electroencephalogram (EEG) showed diffuse paroxysmal discharges accompanied by sharp-wave complexes and valproate therapy was started. Computed tomography (CT) of the brain was normal. Because of persistent seizures, the girl was admitted to the hospital. CSF analysis revealed the IgG synthesis within the central nervous system (CNS) with oligoclonal bands of immunoglobulins. Repeated CT of the brain revealed diffuse atrophic changes. Despite being on valproate therapy she experienced no improvement. The girl's condition continued deteriorating. She became soporiferous and tetraparetic. The disease had a fulminant course and the girl died in December 2002. Her identical twin sister also had a morbilliform rash at the age of six months but she didn't exhibit any symptoms of SSPE until the end of 2004.

Patient 2

Patient 2 was born in November 1994 in a normal pregnancy. He was vaccinated regularly with the MMR-vaccine[8]. At the age of seven months, the boy had a febrile disease with morbilliform rash. During 1995, he was hospitalized on three occasions for febrile convulsions for which he was placed on prophylactic therapy with phenobarbitone. In October 1996, the boy was readmitted to the hospital for relapsing convulsions. Because of multifocal EEG discharges, he was placed on valproate therapy. In September 2001, he entered the primary school. Eight months later, mental deterioration started accompanied by memory dysfunction, dysgraphia and dyslexia. Two months later, he developed ataxia and was admitted to the hospital. EEG revealed hypsarrhythmia. CSF analysis revealed the IgG synthesis within the CNS with oligoclonal bands of immunoglobulins. CT of the brain was normal. A topiramate therapy was started. During the hospitalization, he still occasionally had partial seizures in the extremities accompanied by short losses of consciousness and absences. His condition continued deteriorating. The patient was unable to sit voluntarily, stopped talking and lost control of the sphincters. As the disease was progressive, the boy died in January 2003.

Patient 3

Patient 3 was born in May 1990 in a normal pregnancy. He was vaccinated regularly with the MMR-vaccine[8]. At the age of six years, he had the first partial seizure. The EEG revealed dysrrhythmic discharges and a therapy with primidone was started. In March 2002, he was hospitalized for varicella when the first generalized seizure occurred. On an EEG, irritative bilateral changes were then detected. CT of the brain was normal. Five months later, his mother noted changes in his behavior, ataxia and occasionally indistinct speech. The boy was readmitted to the hospital. At the end of August 2002, he developed the signs of milder respiratory infection. The following day he became febrile and markedly somnolent, waking up only at a stronger stimulus. Repeated EEG showed generalized dysrrhythmic discharges with paroxysms of high-voltage slow waves and occasional sharp-pointed waves. CSF analysis revealed the IgG synthesis within the CNS with oligoclonal bands of immunoglobulins. MRI of the brain was normal. On several occasions during the hospitalization, he suffered from generalized convulsions. A therapy with phenobarbitone and carbamazepine produced no improvement. The disease had a progressive course and the boy died in November 2003.

Patient 4

Patient 4 was born in November 1997 in a normal pregnancy. He was vaccinated regularly with the MMR-vaccine[8]. The patient developed varicella in October 2002. On the third day of the disease, his mother noted his head dropping down on several occasions. The patient was hospitalized and treated with acyclovir intravenously. Then ataxia and myoclonic seizures of the arm and head developed. The treatment with carbamazepine resulted in temporary improvement. Next dyplopia arose accompanied by dysarthria, swallowing difficulties and inability to control the sphincters. EEG showed continuous slowness with paroxysmal discharges. CSF analysis revealed the IgG synthesis within the CNS with oligoclonal bands of immunoglobulins. On brain MRI, discrete hyperintensive lacunar regions subcortically in white matter were found. During hospitalization he was treated with phenobarbitone and carbamazepine but no improvement was observed. Due to progressive disease, the boy died in December 2003.

Methods

Serologic testing of serum and CSF samples for MV and for varicella zoster virus (VZV)-specific antibodies was performed at WHO National Measles Laboratory, Croatian National Institute of Public Health (CNIPH). Antibody titer was determined by using the complement fixation (CF) test (micromethod)[9] and enzyme-immunosorbent assay (Measles Virus-EIA, Institute Virion; Anti-VZV-ELISA, Euroimmun). Antigen used in CF test was obtained from Edmonston strain of MV at Virology Department, CNIPH[9]. Guinea-pig complement and haemolysin were prepared commercially at the Institute of Immunology, Zagreb. Brain tissue samples of two patients obtained at autopsy were examined by light microscopy, electron microscopy (EM; Neuropathology Department, Clinical Hospital Centre, Zagreb) and indirect immunofluorescence (IFA – Measles IFA Kit, Light Diagnostics; Virology Department, CNIPH).

Results

In 2002, SSPE was diagnosed in four patients (three boys and one girl) in Croatia. Their age at disease onset ranged from 5–11 years. They all had been vaccinated regularly against measles according to the official immunization schedule[8]. Two had a history of measles infec-

TABLE 1
CLINICAL AND EPIDEMIOLOGICAL DATA OF FOUR SSPE PATIENTS

Patients	Sex	Year of birth	Place of birth	MMR-vaccination /revaccination (age)	Measles infection (age)	Date of SSPE onset	Age at diagnosis	Duration of disease
1	F	1997	Požega	13 mo / –	6 mo (morbilliform rash)	August 2002	4 yr 8 mo	4 mo
2	M	1994	Koprivnica	20 mo (only measles) / 6 yr	7 mo (morbilliform rash + fever)	May 2002	7 yr 6 mo	8 mo
3	M	1990	Rovišće	12 mo / 11 yr	–	August 2002	11 yr 3 mo	15 mo
3	M	1997	Garčin	12 mo / –	–	October 2002	4 yr 11 mo	14 mo

mo – months

TABLE 2
LABORATORY AND HISTOPATHOLOGIC FINDINGS OF FOUR SSPE PATIENTS

Patients	Complement-fixing test CSF / serum			EIA – IgG CSF / serum		Electron microscopy (brain tissue)	IFA (brain imprint)
1	I	1:128	1:32768	positive	positive	autolysis, without MV nucleocapsids	positive
	II	1:128	1:65536	positive	positive		
2	I	1:16	1:4096	positive	positive	intranuclear inclusions (MV nucleocapsids) in neurons and astrocytes	positive
	II	1:32	1:4096	positive	positive		
3	I	1:16	1:1024	positive	positive	–	–
4	I	1:32	1:2048	positive	positive	–	–

tion (diagnosed clinically) at the age of six and seven months, respectively (Table 1). In the other two patients, the disease began immediately after varicella infection. We detected antibodies to MV in the CSF and serum of all patients. The CF-antibody titers ranged from 1:1024 to 1:65536 in serum and from 1:16 to 1:128 in CSF (Table 2). In CSF, no antibodies to VZV were found. For two patients brain tissue was obtained post mortally. Using IFA, the MV antigen was detected in the brain imprints of both patients (Table 2). The histopathologic examination of the brain tissue from the second patient revealed neurofibrillar degeneration with acidophil intranuclear inclusions in the neurons (Figure 1a) and glial cells (Figure 1b). Using EM, intranuclear viral inclusions composed of MV nucleocapsids were demonstrated (Figure 1c and 1d). Strong autolysis prevented finding the characteristic changes in the brain tissue from the first patient (Table 2).

Discussion

The incidence of acute measles infection and SSPE has been dramatically reduced because of the widespread administration of measles vaccine. Despite vaccination, mainland Croatia had two measles outbreaks in the past ten years with 697 and 648 cases notified in 1995 and 1998, respectively (data from Reference Epidemiology Centre, CNIPH). The last registered SSPE case before those reported in the present study dates from 1994.

Studies involving the genetic characterization of viral material from brain tissue of SSPE patients have all reported the wild type MV[10–13]. In plasma, serum and CSF samples of our patients, the RT-PCR revealed no viral RNA. Only brain tissue samples from both of them were positive. The nucleotide sequence analysis showed that viruses detected from the brain tissue belong to the wild-type MV D6 genotype[14].

In spite of some reports of SSPE occurring after the administration of the MMR vaccine[3, 15], there is no evidence that the measles vaccine could cause SSPE (no vaccine strain has ever been discovered). Similarly, no increased risk associated with the administration of a measles vaccine to the children who had already had measles was observed[16]. It is likely that SSPE cases with no history of natural measles infection may have resulted from a subclinical or unrecognized infection that occurred before the administration of vaccine[17]. Before the routine use of measles vaccine, Krugman et al. reported finding that 15–20% of the children whose parents had reported no history of measles were immune to this disease. These children presumably were exposed at a time when maternal antibodies modified the disease but did not prevent asymptomatic or non-specific infection[18]. The other possibility of SSPE in vaccinated individuals is due to poor seroconversion or vaccine failure. This could happen either due to poor quality of vaccine or to its administration at an earlier than the recommended age at 12–15 months[19].

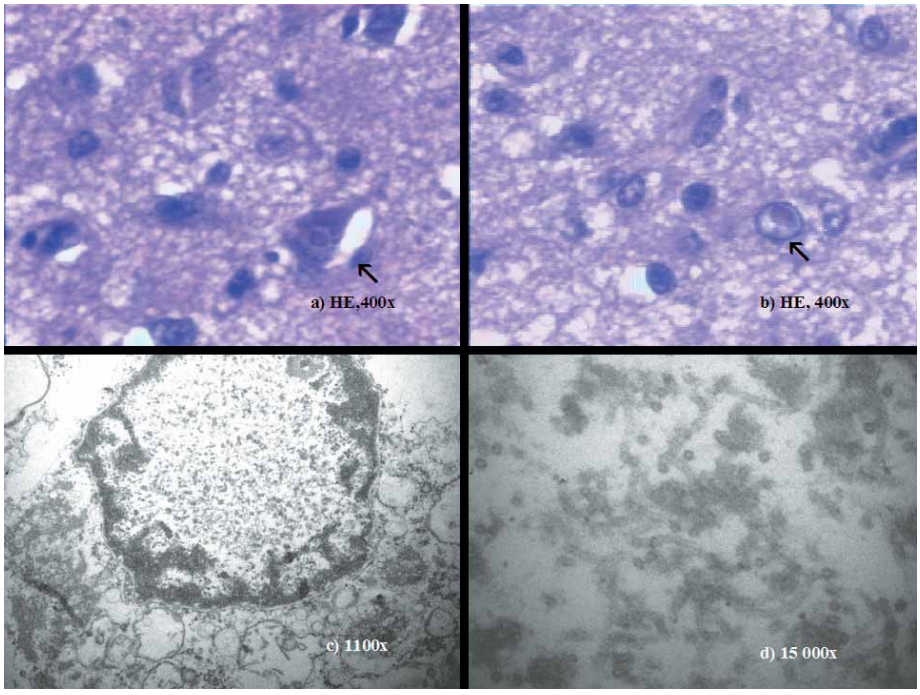

Fig. 1. Neuron contains eosinophilic nuclear inclusion (a), nuclear inclusion is also in glial cell (b). On electron microscope analysis, intranuclear viral inclusions are composed of measles virus (MV) nucleocapsids (c and d).

In 2002 in northwest Croatia, an exceptional cluster of four SSPE patients was diagnosed in a 6-month period. They all were vaccinated regularly against measles at an age of 12–20 months[9]. Two patients had measles as infants at the age of six and seven months, respectively, during the 1998 and 1995 measles outbreaks. In both patients, the disease was diagnosed retrospectively after taking detailed medical histories, but was no serologic confirmation. No vaccine strain was detected in the brain tissue although both these patients were immunized after a natural measles infection. According to the reports of other authors[10–13], they have been infected with the wild-type MV before vaccination[14]. In the other two cases, the disease began immediately after a varicella infection. No antibodies to VZV were found in the CSF of these patients. Anlar et al. have investigated the hypothesis of other viruses contributing to the pathogenesis of SSPE. They tested the CSF of 43 SSPE patients for DNA, RNA and antibodies against several viruses, VZV included, comparing them with those from 39 patients with other non-infectious neurological disorders. Forty-one point eight percent of SSPE patients had antibodies to more than one virus synthesized intrathecally. VZV DNA was found in 11.6% patients with SSPE compared to 15.3% in controls. Likewise, antibodies to VZV were present in 10.2% of SSPE patients and in 10.0% of controls. Their data do not support a specific role for this agent in SSPE[20].

Although the pathogenic mechanisms that result in SSPE following measles are not understood, several theories are proposed. One theory holds that affected patients have a hyperimmune response[21] resulting in antibodies masking the infected cell surface antigens and making them unrecognizable to cytotoxic T-cells[2]. Another theory suggests that neurons and glia fail to envelope and transport the antigen to the membrane, leading to an inability by the immune system to recognize infected cells[22].

There have been several reports in the literature about SSPE in twins. Vieker at al.[6] reported the occurrence of SSPE in two brothers two years after measles infection. The occurrence of two cases in one family is suggestive of a genetic predisposing factor. In contrast, Dhib-Jalbut and Haddad[23] described SSPE in one member of identical twins that emphasizes the importance of other factors in the pathogenesis of SSPE. One our patient was born in a twin-pregnancy. Her identical twin sister was also vaccinated against measles after a natural measles infection at the age of six months but she didn't exhibit any symptoms of SSPE.

Because SSPE reporting to the Epidemiological Service in Croatia is not obligatory, its incidence is unknown. This study describes a cluster of four SSPE patients in 2002 in Croatia, after an eight-year interval with none reported. The last notified diagnosed case of SSPE was a 10-year old girl in 1994. She had a short period of disease progression, but remained stable long thereafter. Still alive, she suffers from severe neurological defects (spastic tetraparesis, blindness and aphasia). The rate of SSPE in Croatia during observing period is higher than reported worldwide. We suppose that many

cases of measles were missed or not reported to the Epidemiological Service during the epidemics.

In conclusion, we feel that all SSPE case reporting should be mandatory and supported by laboratory confirmation and molecular characterization of the MV strains. In addition, all cases of febrile disease accompanied by morbilliform rash in early childhood in the differential diagnosis should consider measles.

Acknowledgements

This study was run as part of the Croatian Ministry of Science and Technology project 0005 002 (GM-G). The authors thank Vladimira Kružić, MD, MSc for substantial contribution in preparing the manuscript. The authors thank Ljiljana Katičić, Ljiljana Milašinčić, Snježana Artl and Monika Penava, med.lab.ing. from the Virology Department, CNIPH for help with serologic tests.

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SUBAKUTNI SKLEROZIRAJUĆI PANENCEFALITIS: STALNA PRIJETNJA

SAŽETAK

Analizirani su klinički, epidemiološki i laboratorijski nalazi četvero bolesnika sa subakutnim sklerozirajućim panencefalitisom (SSPE) u Hrvatskoj tijekom 2002 godine. Dob bolesnika iznosila je od 5–11 godina. Svi su bolesnici redovno cijepljeni protiv morbila (Morbili-Parotitis-Rubela cjepivo). Dvoje bolesnika je imalo anamnestički podatak o preboljelim morbilima u dobi od šest odnosno sedam mjeseci. U druga je dva bolesnika bolest počela neposredno nakon preboljelih vodenih kozica. Titar komplement-fiksirajućih protutijela na virus morbila (MV) iznosio je od 1:1024 do 1:65536 u serumu te od 1:16 do 1:128 u cerebrospinalnom likvoru (CSL). Protutijela na virus varicella-zoster u CSL nisu nađena. Postmortalno su dobiveni uzorci moždanog tkiva od dvoje bolesnika. U jednog je bolesnika elektronska mikroskopija pokazala intranuklearne virusne inkluzije (MV nukleokapside). Metodom IFA, MV antigen dokazan je u moždanom otisku u oba bolesnika. Virusna RNA nađena je samo u uzorcima moždanog tkiva, dok su plazma, serum i CSL bili negativni. Analizom sekvenci nukleotida dokazan je divlji tip MV D6 genotipa[14].