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PREGLED
REVIEW

SUBACUTE SCLEROSING PANENCEPHALITIS

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Subacute sclerosing panencephalitis is a manifestation of persistent measles virus infection in the brain. It affects about 1/10 000 children who experience natural measles infection, but the risk is about 10 times higher if measles infection occurs below 1 year of age. Recent measles epidemics in central Europe will bring the possibility of this complication into consideration in the future. The diagnosis of subacute sclerosing panencephalitis should be considered in a child, adolescent or young adult with behavioral changes, myoclonia, forgetfulness, or deterioration of cognitive functions developing over weeks or months. Electroencephalogram is typical and measles antibody titers in the cerebrospinal fluid are diagnostic. Treatment includes immunomodulatory and antiviral agents, but results in relative remission or stabilization in less than 30% of patients. The fact that spontaneous remissions are also observed suggests host immunity as the main factor affecting outcome; therefore, supportive care and immunomodulatory agents constitute principal aspects of treatment.

Descriptors: MEASLES; ENCEPHALITIS; MYOCLONUS; SUBACUTE SCLEROSING PANENCEPHALITIS

INTRODUCTION

Subacute sclerosing panencephalitis (SSPE) is chronic encephalitis due to measles virus (MV) infection. It manifests 1-10 years after acute measles infection encountered in childhood, usually early childhood or infancy. Its pathogenesis is unclear; current knowledge supports the persistence of MV in the host after primary infection, probably in the lymphoid or nervous tissues. MV can persist in the nervous system, spreading trans-synaptically and undergoing mutations during this stage (1). These mutations may alter the receptor specificity of the virus, allowing entrance to the cells inaccessible to the wild-type virus (2).

The severity of acute measles infection is not a factor influencing persistence of MV; even subclinical measles without rash may result in SSPE. In fact, a considerable proportion of measles infections, particularly those developing in partially immunized hosts, are not associated with rash and therefore likely to be undiagnosed and unreported (3, 4). This is also one of the reasons the vaccine virus (and not measles virus) has been erroneously implicated in certain SSPE cases. Another reason for SSPE being attributed to the vaccine is the possibility of low seroconversion rates, i.e. the host's inability to synthesize protective titers (vaccine failure). However, SSPE does not develop with the vaccine virus. Molecular studies on brain tissue from SSPE patients have consistently shown the wild-type MV circulating during the patient's encounter with measles (5, 6). Measles epidemics in central Europe in recent years create a need for follow-up in the future.

The persistence of MV may be facilitated by the presence of low-titer antibodies, as in infants carrying maternal anti-MV antibodies. Experimental work also supports this hypothesis: mice treated with immunoglobulin after inoculation with MV developed subacute encephalitis, while those untreated underwent acute fatal encephalitis (7). The mutations observed in the virus recovered from SSPE patients probably result from the persistence. As the mutations accumulate during the latent period, they impede normal maturation of the virus, preventing recognition by host cellular and humoral immunity. The MV thus escapes immunity and is able to prolong its persistence.

SSPE usually manifests in childhood or adolescence and rarely in young adults. The estimated incidence is 1/10 000 measles cases. This rate is higher, up to 1/1000, in infants. There is a male predilection (M/F ratio: 1.7/1). The age at onset varies in time: in Turkey, it was a mean of 12 years until 1989, when a decline to a mean of 7.6 years was observed during the 1990-2000 period (8). Currently, the mean age is 12-13 years again (unpublished data). Interestingly, this fluctuation cannot be attributed to changes in the age at primary measles infection, which remained around age 1 year in SSPE patients during these two decades. However, a recent paper from Japan states the earlier measles infection is encountered, the younger is the onset of SSPE (9).

Genetic studies of cytokine gene polymorphisms showed no consistent findings (10, 11). This can be expected because very few siblings are affected; those reported so far are probably due to exposure

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to measles simultaneously at an early age.

Immune and degenerative mechanisms have been examined in SSPE; individual differences in these mechanisms may explain variations in clinical symptoms and course among patients (12-16).

SYMPTOMS IN SSPE

The majority of patients present with negative or positive myoclonia such as head dropping, frequent falls, or focal myoclonia on the face and arm. Staging based on the symptoms and signs is useful for clinical follow-up. Stage 1 consists of mental regression, behavioral changes, and school failure; stage 2, myoclonia as described above, but ability to walk with or without support; and stage 3, bed- or wheelchair-bound state. The diagnosis is most frequently made in stage 2, which is more recognizable by parents, while symptoms of stage 1 are usually attributed to psychological factors and school problems.

A pediatric neurologist should consider SSPE when facing a 5- to 15-year-old who had shown normal development until recently and who presents with a few weeks or months history of ataxia, forgetfulness, behavioral abnormalities, brief attacks of loss of tone, or myoclonia.

Less typical presentations occur in 20%-30% of patients, and may lead to misdiagnoses even by the most experienced clinician (17): Seizures, which can be diagnosed and treated as primary epilepsy for as long as 1-2 years;

Hemiparesis or hemidystonia, which is usually investigated for mass, stroke, or demyelinating disease;

Personality changes and introversion, which usually lead the parents to seek advice of a psychologist of psychiatrist; and

Vision loss, which can be due to measles virus retinopathy or cortical lesions of SSPE (18).

DIAGNOSTIC TESTS

Electroencephalogram (EEG) should be obtained both awake and after the intravenous injection of diazepam. Periodical high amplitude slow waves or sharp waves appearing as generalized bursts are a typical finding of SSPE (Figure 1). They are not suppressed after the injection of diazepam, unlike other epileptic discharges. They can be as infrequent as 1-2 bursts in 5 minutes, or as many as one every 5-10 seconds. On the other hand, in some cases, especially early in the disease, routine EEG can be normal and periodical waves appear only after diazepam, becoming more visible after the background rhythm is suppressed by the drug. Therefore, the administration of diazepam is useful both in the diagnosis and differential diagnosis (see below).

The definitive diagnosis of SSPE depends on measles IgG titer measured by enzyme immunoassay (EIA) and enzyme-linked immunosorbent assay (ELISA), and the measles IgG synthesis index in cerebrospinal fluid (CSF). These tests are very specific; there are no false positives except for low-titer measles IgG in multiple sclerosis and certain autoimmune conditions. In SSPE, the titers are as high as 4-9 mu/mL (negative: <1 mu/mL) and the measles IgG synthesis rate (index) is markedly elevated. The CSF contains oligoclonal bands and the total IgG index is also markedly elevated, among the highest in neurologic diseases.

Magnetic resonance imaging (MRI) is not needed for diagnosis but for differentiation from other disorders listed below. MRI is frequently normal in the first few months. Later, periventricular white matter signal intensity changes on T2-weighted images are the most frequent type of abnormality. Atrophy develops in 1-2 years (19).

DIFFERENTIAL DIAGNOSIS

Epilepsy, especially progressive myoclonic epilepsy (PME), can mimic SSPE. The main differences are the presence of a family history and slower mental deterioration in PME, and EEG findings where the epileptic discharges are at least partially suppressed with diazepam. In addition, myoclonia in SSPE, unlike PME, improves with carbamazepine.

Sydenham's chorea: irregular limb movements, loss of coordination, and dysarthria in SSPE may be mistaken for chorea in a school-age child.

Degenerative/metabolic neurologic disorders: leukodystrophy and neuronal ceroid lipofuscinosis are associated with progressive neurologic deterioration and require EEG, MRI, and CSF analyses for differentiation.

Space occupying lesions: when SSPE presents with unilateral paresis or dystonia, focal intracranial lesions can be considered.

Increased intracranial pressure: SSPE itself may present with increased intracranial pressure, and other causes of pseudotumor cerebri might be investigated until the diagnosis of SSPE is made.

Wilson's disease: dystonia, hand tremor and ataxia are possible manifestations common to both Wilson's disease and SSPE.

Multiple sclerosis: in adults, SSPE tends to manifest with focal subacute neurologic symptoms such as vision loss or

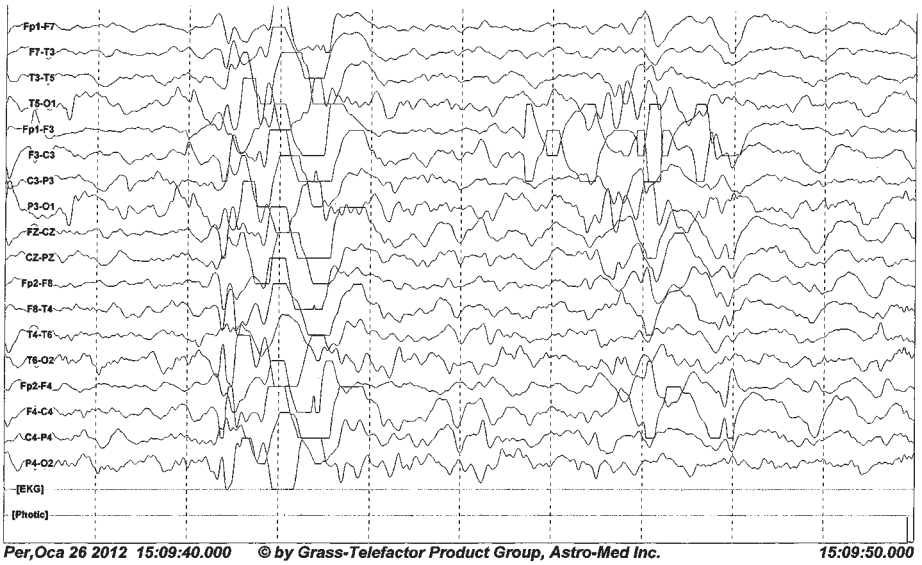

Figure 1. *Typical EEG of SSPE: generalized high amplitude, slow sharp wave on a slow background rhythm. The background can be normal at earlier stages.*
Slika 1. *Karakterističan EEG zapis kod SSPE: generalizirani polagani oštar val visoke amplitude na polaganom pozadinskom ritmu. Pozadina može biti normalna u ranijim stadijima bolesti.*

unilateral tremor. Focal signal intensity changes may suggest multiple sclerosis, especially because of the frequency of this disorder in young adults.

Acute viral encephalitis: the fulminant type of SSPE can present with seizures and loss of consciousness, mimicking, and sometimes treated for, acute encephalitis.

Variant Creutzfeldt-Jacob disease: myoclonia and deterioration are typical for this disease and SSPE. MRI findings differ.

Subacute measles encephalitis: it is due to measles virus infection in immunocompromised hosts, where myoclonia, progressive mental deterioration and vision loss are observed over weeks or months. CSF usually does not contain measles IgG because of the immune status of the patient. EEG may resemble SSPE. The diagnosis is based on the history of measles and immunosuppressed state (20).

Conversion disorder: this is a diagnosis of exclusion but, especially in low-incidence areas, the possibility of SSPE may be overlooked and erroneously diagnosed as conversion disorder.

CLINICAL COURSE

SSPE is generally progressive, from stage 1 to stage 2 in 1-6 months and from stage 2 to stage 3 in 6-12 months. Spontaneous remission has been observed in 5% of untreated patients. Therefore, the diagnosis of SSPE should not be considered as a death certificate, and attempts should be made towards increasing this rate as well as the quality of life.

TREATMENT

Today's measures can provide stabilization and some improvement in about 30% of cases. The exact duration of this effect is unknown, but has been observed to last for more than one decade.

The incidence of SSPE is not high enough, and its course not standard enough to have randomized trials. It is not possible to detect small differences obtained with a particular treatment. Moreover, the large patient series required for randomized trials are impossible to collect even by multicenter studies. Therefore, treatment modalities have been tried in small case series, compared to historical or contemporary controls who received other treatments.

Therapeutic agents are chosen according to the child's age, clinical condition, and the availability of the drug. Oral inosiplex is a safe immunomodulatory drug that is easy to administer and has shown some efficiency in controlled studies when compared to untreated cases. It is given at a dosage of 50-100 mg/kg in doses divided as practically possible.

Some patients have been reported to benefit from interferons. Most publications are case series. The benefit rate is around 30%. Alpha- and beta-interferon have been used in clinical trials or case series. Alpha interferon has been given by parenteral route and also intracerebrally. The best results have been obtained with human natural alpha interferon given intraventricularly in combination with oral inosiplex; the rates of stabilization were 50% (21, 22). Recombinant interferon has not produced results superior to inosiplex alone (23).

Beta interferon is easier to administer. In one retrospective study, it prolonged survival and ambulation (24).

Antivirals

Ribavirin has been given intraventricularly, and MV IgG titers diminished in some patients although no clear clinical benefit was observed; some of the patients were already undergoing a chronic course (25). Patients treated late in the disease inevitably bias the study group because they represent a subgroup of SSPE with slower course.

Steroids, plasmapheresis, and rituximab, as expected in a disease where robust immune reponse is needed, are useless and may even hasten the progression of the disease (26, 27). On the other hand, intravenous immunoglobulin may lead to short-term improvement and can be indicated in acute worsening usually precipitated by nonspecific respiratory infections (28).

Symptomatic treatment

The myoclonia of SSPE, in contrast to other myoclonia of various etiologies, responds to carbamazepine. Therefore, it is the drug of choice in the beginning. The cessation of myoclonia within a few days remedies the gait and balance problems for a few months to years. Generalized seizures can occur in later stages and can be difficult to distinguish from tonic spasms by history only; in this case, antiepileptic medication can be used, including levetiracetam, valproate, or phenytoin. Spasticity and sleep disturbances are symptoms of stage 3 and may benefit from clonazepam and baclofen. Fever is frequent in SSPE patients, either due to secondary urinary or respiratory infection, dental infection, or, in stage 3, due to the disease itself. In case of fever, a general practitioner or pediatrician should search for common infectious causes. Fever due to SSPE is persistent and usually high, with only partial response to antipyretics. In this case, myorelaxants and clonazepam can be of benefit in addition to antipyretics.

Physiotherapy

It should be started in early stages of the disease, before the movements of the patient become limited. However, even bedridden patients benefit from physiotherapy, firstly because increased mobility even in the bed facilitates patient care and prevents bed sores, respiratory complications, constipation and painful contractures, but also because some functions that have been lost can be regained. Physical therapy measures include positioning, passive movements, induced movements, thoracic percussion, and when necessary, the adjustment of ortheses.

PREVENTION

The only and efficient preventive measure is widespread immunization against measles. Starting at the age of 12 months, or 9 months in case of epidemic, two doses of vaccine should be given to all children. Vaccine-induced immunity tends to wean and antibody titers tend to fall after 10 years; therefore, mothers who had been vaccinated during their childhood may not possess protective IgG levels for their infants. Because measles in early infancy is associated with an increased risk of SSPE, re-immunization of young adults may be considered in areas where exposure to imported or endemic virus is likely.

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Authors declare no confilct of interest.

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S a ž e t a k

SUBAKUTNI SKLEROZIRAJUĆI PANENCEFALITIS

B. Anlar

Subakutni sklerozirajući panencefalitis je manifestacija tvrdokorne infekcije virusom ospica u mozgu. Zahvaća jedno na 10 000 djece s infekcijom ospica, ali je rizik oko 10 puta veći ako se ospice pojave u dobi mlađoj od jedne godine. Zbog nedavnih epidemija ospica u centralnoj Europi ubuduće ovu komplikaciju treba smatrati mogućom. Dijagnozu subakutnog sklerozirajućeg panencefalitisa treba uzeti u obzir kod djeteta, adolescenta ili mlade odrasle osobe s promjenama ponašanja, mioklonijom, zaboravnošću ili pogoršanjem spoznajnih funkcija, koje nastaju tjednima ili mjesecima. Elektroencefalogram je znakovit, a titar antitijela na ospice ima dijagnostičku vrijednost. Liječenje uključuje terapiju imunomodulatorima i protuvirusnim lijekovima, ali dovodi do relativne remisije ili stabiliziranja u manje od 30% bolesnika. Bilježe se i spontane remisije, što ukazuje na to da je imunitet domaćina glavni čimbenik ishoda; stoga su potporna skrb i imunomodulatori glavni oblici liječenja.

Deskriptori: OSPICE; ENCEFALITIS; MIOKLONUS; SUBAKUTNI SKLEROZIRAJUĆI PANENCEFALITIS

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