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Subacute Sclerosing Panencephalitis (SSPE) in a 10 ½ Year Old Male Child

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ABSTRACT

Subacute sclerosing panencephalitis (SSPE) is a progressive neurological disorder of childhood and early adolescence, caused by persistent defective measles virus. A 10 ½ year-old male child with h/o having normal milestones till the age of 15 months had an episode of measles for which child was hospitalized. After one year he showed gradual deterioration of already attained milestones but continued regression of milestones noticed, presented to the department at 10½ years with h/o not getting up from the bed. Patients usually have behavioural changes, myoclonus, dementia, visual disturbances, and pyramidal and extrapyramidal signs and can cause death within 1-3 years of presentations. The diagnosis is based upon characteristic clinical manifestations, the presence of characteristic periodic EEG discharges, and demonstration of raised antibody titre against measles in the plasma and cerebrospinal fluid. Treatment for SSPE is being researched. A combination of oral Isoprinosine and intraventricular interferon alfa appears to be the best effective treatment. Patients responding to treatment need to receive it lifelong. At present effective measles vaccination is the only solution to SSPE.

Keywords: SSPE, Measles, Vaccination.

1. INTRODUCTION :

Subacute sclerosing panencephalitis (SSPE) is a disorder of the central nervous system, a slow virus infection caused by defective measles virus. Greenfield suggested it in 1960 to designate a condition due to a persistent infection by a virus involving both grey matter and white matter [1]. Dawson, for the first time, described a child with progressive mental deterioration and involuntary movements who, at a necropsy, was found to have a dominant involvement of grey matter in which neuronal inclusion bodies were abundant [2] using the term “subacute inclusion body encephalitis”. Later Pette and Doring (1939) reported a single case, called “nodular panencephalitis” having equally severe lesions in both grey and white matter [3]. Van Bogaert noticed the presence of dominant demyelination and glial proliferation in the white matter and coined it “subacute sclerosing leukoencephalitis”[4]. Bouteille et al, in 1965, on electron microscopy

demonstrated structures resembling measles virus in the brain [5]. In 1969 measles virus isolation was done from the brain of a patient with SSPE [6].

2. CASE REPORT :

A 10 ½ year old male child with h/o having normal milestones till the age of 15 months had an episode of measles. After one year he showed gradual deterioration of already attained milestones, after one year presented to the department with h/o not getting up from the bed. His mother noted personality changes of irritability and worsened attention. Several months later, he developed intermittent, random, low-amplitude, lightning-like jerking movements of the extremities. During the next several months, the boy became increasingly withdrawn and emotionally weak. He was treated for depression, but fluoxetine induced a marked worsening of the movement disorder and was discontinued. He was next treated with valproic acid, which worsened the movement disorder and no improvement in the

psychiatric symptoms. Although the boy's academic performance had previously been average, he began to fail academically. He lost previous mathematics and language skills, and his teachers and parents noted progressive memory deficits. The movement disorder evolved from random myoclonic jerks of all four extremities to drop attacks many times a day, during which, while walking or standing, he would suddenly fall to the floor. Parents had consulted many doctors for the treatment. But there was continued regression of milestones.

No h/o altered sensorium, diplopia, vomiting. Family history was unremarkable.

General physical examination: The child was bedridden.

Anthropometry revealed

Height: 154cms, Weight: 30Kg, HC: 50CMS

CNS examination showed he was alert and cooperative; posture restricted to the bed, but produced little spontaneous or prompted speech. He followed simple verbal commands, but had difficulty with more complex ones and appeared confused by simple written commands. On Cranial nerve examination, saccadic pursuit movements of gaze, hypometric saccades, and mild facial diplegia. Motor examination revealed cogwheeling in the upper extremities bilaterally, especially on pronation-supination. The posture and stance were remarkable for intermittent shock like dipping of the head and shoulders with no apparent change in level of consciousness or postictal state. Systemic examination revealed normal RS, CVS and PA.

Investigations revealed that CBC, chest x-ray, serum electrolytes, CPK were all within normal limits. Magnetic Resonance Imaging (MRI) showed focally abnormal with a single patch of increased T2 signal intensity and decreased T1 signal intensity in the subcortical white matter of the frontal lobe. The focal lesion did not enhance with gadolinium. Electroencephalogram (EEG) revealed high-amplitude bursts of periodic slow-wave complexes every 4–10 seconds, often accompanied by observable axial myoclonic spasms. The periodic slow-wave complexes arose from background activity that was essentially normal, except for some mild bi frontal dominant slowing. Burst suppression was also seen. Cerebrospinal fluid (CSF)

cytology, glucose, and total protein levels (15 mg/dL) were normal, but CSF immunoglobulin G (IgG) was elevated at 16.5 mg/dL (normal, 0.5–5.9 mg/dL.) Measurement of specific antibodies by enzyme-linked immunosorbent assay revealed that rubeola (measles) IgG antibodies were markedly elevated in the CSF at 1:320 (normal, <1:5) and in the serum at 1:5560. Both the EEG and CSF patterns were pathognomic for SSPE and that diagnosis was made.

The child was given the following treatment, was subjected to multidisciplinary management, physiotherapy, neuro rehabilitation and occupational therapy. The child was put on Isoprinosine 100mg/kg/day. Parental counselling was given. The child did not improve during hospitalisation.

3. DISCUSSION :

Epidemiology

The SSPE has declined because of effective measles vaccination. Saha et al. reported an annual incidence rate of 21 per million population in India, in comparison to 2.4 per million population in Middle East. Most patient give history of primary measles infection at an early age (< 2 years), which is followed after a latent period of 6 to 8 years by the onset of a progressive neurological disorder. Children who get measles below age of 1 year carry a risk of 16 times more than those infected at 5 years or later. A higher incidence (male/female ratio 3:1) has been noted in rural children than city children, children with two or more siblings, children of lower socio-economic status, and mentally retarded children. Neither the age of exposure to measles, nor severity of infection seem to affect the age of onset of SSPE or course of the disease. Universal measles vaccination has produced greater than 90% reduction in the incidence of SSPE in developed nations. In vaccinated children prolongation of age of onset and latency of infection had been observed. There is no revealed evidence to suggest that attenuated vaccine virus is responsible for sporadic cases of SSPE (Dawson's disease).

Pathogenesis:

SSPE virus is distinguished from the wild type of measles virus in that there appears to be a

defect in assembly of the virus within the nervous system, and which is related to an abnormality of matrix of 'M' protein of the virus. Studies that show that the matrix protein is the only structural protein which is undetected in brain cells from patients with SSPE, and on observation of a selective decrease in antibodies to the matrix protein in these patients.

Studies on SSPE cell lines further suggest that the M protein may be synthesized but fails to accumulate and there may be defective translation of matrix messenger RNA. An immune response can be made against the viral hemagglutination resulting in very high levels of neutralizing antibody, and yet the antibody is ineffective in eradicating the virus. So, M-protein is necessary for correct assembly of progeny virus at the surface of infected cells, mutations in this protein lead to an antigenically distinct form that can no longer bind to viral nucleocapsid that initiate virus maturation. The absence of functionally intact, budding virus particle, results in intracellular accumulation of incomplete measles virus in brain cells (7-12)., Modulation of measles antigen on the surface of infected cells by antimeasles antibody is seen, and the modulation might make the cell vulnerable to attack by the immune system and could alter expression of virus within the cells. Antigenic challenge of a second infection may alter the dormant state of SSPE virus and manifest in disease expression. Sero-epidemiological data suggest that an exposure to another virus, such as Epstein-Barr virus or influenza type I virus may transform the measles virus into a defective virus (Dawson) [9].

Diagnosis:

The clinical course has been arbitrarily divided into several stages. The first stage is characterized by an insidious onset of dementia and changes in behaviour, and the child often presents because of a deteriorating school performance. Progression to the second stage is initiated by motor dysfunction with both pyramidal and extrapyramidal signs. Myoclonic jerks are usually present and convulsions can occur. In the third stage the patient shows progressively decerebration with increasing rigidity and a declining level of consciousness. Death usually within 1-3 years

but may be delayed several months or even years. This is the fourth stage, a temporary arrest in the continuous progress of the disease.

Stage I. Progressive mental changes.

Stage II. Motor dysfunction, Myoclonic jerks, Convulsions.

Stage III. Rigidity, Progressive decerebration and coma.

Stage IV. Death

Electro-encephalogram characteristically shows high voltage slow wave complexes across all leads. They occur regularly at 3.5 to 20 sec intervals and are often synchronous with the myoclonic jerks. Measles serology is an essential diagnostic tool. The most important single diagnostic criterion for SSPE is the finding of a low CSF: serum ratio of measles antibody. In normal control patients this is between 1/200 and 1/500 (Clarke et al.). Although increased permeability of the blood/brain barrier occurs in some other inflammatory conditions (Sherwin et al. [15]) the CSF antibody levels do not reach the values seen in SSPE, and the CSF: serum ratio remains high. Brain histology is the least important criterion and it is unnecessary to perform a brain biopsy to make a diagnosis of SSPE.

Treatment

No adequate therapy is currently available for the patients of SSPE. Some non randomized studies revealed that certain immunomodulator anti-viral agents can prolong life if long-term treatment is continued. Extremely variable natural course of SSPE as few patients may have spontaneous prolonged remission (Risk and Haddad) [14].

Treatment with isoprinosine (Inosiplex) remains controversial but has been reported to prolong survival and produce clinical improvement in some patients. This drug is recommended in a daily dose of 100 mg/kg/day and without major side effects. Nunes et al [13]. observed good results combining trihexyphenidyl and isoprinosine in controlling myoclonus refractory to sodium valproate.

Intravenous administration of α -interferon has not proved useful because of poor penetration of blood brain barrier. The modest improvement with intraventricular and intrathecal routes (6 million unit/dose/week) of administration have been observed in small

number of patients (Steiner et al.) [16]. The pathophysiology of natural remissions and relapses in SSPE is unknown. CSF interferon levels are low in these patients. Exogenous interferons suppress replication of virus and also influence immune system. There are early relapses after discontinuing interferon therapy. A prolonged therapy is required for sustained response (Gascon et al. [10]).

Combined use of alpha interferon plus isoprinosine. Anlar et al [8]. observed a higher survival rate in the 22 patients after long term (56-108 months) treatment with intraventricular. alpha-interferon and inosiplex as compared to those who did not receive alpha-interferon regimen. But, it did not affect oligoclonal bands and intrathecal CSF immunoglobulin (IgG) synthesis (Mehta et al.) [12].

In an isolated case report intravenous immunoglobulin was found effective in SSPE when administered along with a prolonged therapy with inosiplex. Further evaluation is required to recommend it for regular management of SSPE (Gurer et al.) [11].

Cimetidine, an H₂-receptor antagonist, was used in SSPE due to its immunomodulatory effect. Anlar et al [7], did not observe any worsening in cimetidine-treated group during the study period.

Symptomatic Treatment is essential in SSPE. The good general nursing care is the most important aspect in the management of SSPE. Anticonvulsants, sodium valproate and clonazepam, are helpful in controlling the myoclonus. If spasticity is marked, baclofen and other drugs are used to treat spasticity.

4. CONCLUSION :

SSPE is a slow virus infection caused by aberrant measles virus. One of the most important limitations in treatment of SSPE is difficulty in recognising early manifestations of disease, when the inflammatory changes are, possibly, still reversible. Treatments available are very costly in developing nations and are available only at a few centres in the world. Moreover, these treatments are not curative and only help in prolonging life. The families of patients with SSPE have a lot of physical, psychological, and economical stresses to endure. A great deal of external support is required for these suffering families

to cope with these stresses. At present effective measles vaccination seems to be the only solution to problem of this dreaded neurological disorder. Effective measles vaccination decreased the problem of SSPE.

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