Case report

Subacute Sclerosing Panencephalitis: A Typical Case but Nearly Misdiagnosed

Subacute Sclerosing Panencephalitis: A typical case but nearly misdiagnosed

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Abstract
Subacute sclerosing panencephalitis (SSPE) is a rare progressive, invariably fatal long-term complication of measles infection. It can manifest three to ten years after the acute infection. It results from mutation in the measles virus protein, and inappropriate immune response. We report the case of a 12 year old adolescent with no past history of measles; but in whom the diagnosis of SSPE was made on the basis of the clinical presentation, electroencephalogram results and the detection of anti measles antibodies in cerebrospinal fluid. SSPE should therefore be considered, in a patient with cognitive impairment and myoclonus in a context where measles is not rare even in the absence of history of measles.

KEY WORDS:
Subacute sclerosing panencephalitis, measles, myoclonic jerks, electroencephalogram, anti measles antibodies.

Résumé
La panencéphalite sclérosante subaigüe (PESS) est une complication à long terme de la rougeole. C'est une complication rare, mais invariablement fatale. Elle se manifeste trois à dix ans après l'infection aigue. Elle résulte d'une mutation dans la protéine de virus de la rougeole associée à une réponse immunitaire inappropriée. Nous rapportons le cas d'une adolescente de 12 ans sans antécédents de rougeole; mais chez qui le diagnostic de PESS a été fait sur la base de la présentation clinique, des résultats de l'électroencéphalogramme et de la détection des anticorps anti-rougeoleux dans le liquide céphalorachidien. Le diagnostic de PESS devrait être évoqué chez un patient souffrant de troubles cognitifs et de myoclonies dans tout contexte où la rougeole n'est pas rare, même en l'absence d'antécédents de rougeole.

MOTS CLÉS
Panencéphalite sclérosante subaigüe (PESS), Rougeole, myoclonie, électroencéphalogramme, anticorps anti-rougeoleux.

INTRODUCTION

Subacute sclerosing panencephalitis (SSPE) is a rare progressive, invariably fatal long-term complication of measles infection [1]. It is a neurodegenerative disease due to persistent measles virus (MV) in the brain. The incidence of measles was 0.9 per 1000 in 2002 [2] and so far no case of SSPE has been described in Cameroon. There was an annual incidence of 21 per million population in India in comparison with 2.4 per million population in the Middle East [3].

It could manifest 3-10 years after the acute infection [4]. The pathogenesis is thought to be due to defects in the gene for M-protein so that packaging and budding of the virion is restricted; antibody modulation and failure of the immune system to contain and eliminate the infection [5, 6, 7] There are four main stages of the disease progression: the first stage consists of intellectual deterioration, behavioural changes and decreased school performance because of agnosias, apraxias, attention problems, irritability, distractibility, and emotional liability. In the second stage, myoclonic jerks appear with seizures and intellectual deterioration. The myoclonic jerks are at first subtle and manifest as a periodic eye blinks or head nods. They later become periodic, manifesting as sudden interruption of gait, the jerks disappear in sleep. In the third stage, there is loss of ability to walk, and then to sit up alone. May develop dystonias or dyskinesias in addition to pyramidal signs. Retinopathy and optic atrophy may develop and severe dementia. In the fourth stage, myoclonic jerks disappear, there is progressive unresponsiveness, with increasing hypotonia and decerebrate rigidity, swallowing and respiratory

difficulties with autonomic dysfunction [5, 8]. The diagnosis is made from the clinical presentation, periodic stereotyped high voltage discharges on the electroencephalogram (EEG), raised gammaglobulin or oligoclonal pattern in the cerebrospinal fluid (CSF) and raised titres of measles antibodies in serum and/or CSF [5]. The treatment of SSPE is symptomatic. There have been several options like subcutaneous interferon-alpha, oral isoprinosine, and lamivudine [9]. However, carbamazepine has been shown to be effective in reducing the myoclonic jerks, even though this is a fatal disease [10].

We report the case of a 12 year old adolescent with no past history of measles; but in whom the diagnosis of SSPE was made on the basis of the clinical presentation, EEG results and the detection of anti measles antibodies in CSF.

CASE REPORT

A 12 year old girl from the South region of Cameroon was admitted in the Pediatric Neurology unit in December 2013. She had been having progressive intellectual deterioration, memory loss and unexplained decline in her school performance 16 months prior to admission. This was closely followed by abnormal, involuntary movements- intermittent, brief myoclonic jerks- first observed on the head, then upper limbs, and then on the lower limbs. She is the second child in a family of five children, and born from healthy parents. Her prenatal and natal histories as well as developmental milestones were normal. She had a unique dose of measles vaccine at the age of nine months, and there was no past history of clinical measles or exanthematous febrile illness. The child was first consulted in the South Regional Hospital, where these symptoms were initially managed as generalized epileptic seizures. The clinical course seemed to have been stable but, within a period of one year she developed an unsteady gait associated with difficulty holding objects with the hand. A second consultation was done, and a cerebral scan done was normal and an EEG was interpreted as showing partial epileptic seizures, and then referred to the pediatric neurologist. Clinical assessment revealed an alert and cooperative patient with periodic drooping of the head. Higher mental functions, cranial nerve testing, muscle strength and tonus were normal. She had an unsteady, wide gait, and myoclonic jerks on the upper limbs and the head. Meanwhile sensitivity and reflexes were normal. There was no cerebellar syndrome, ataxia and trembling.

A second EEG was done and it showed periodic, stereotyped, high voltage discharges which were symmetrical, identical in morphology intervals between discharges. These findings were the same as those noted on the first EEG. On the basis of these finds the diagnosis of subacute sclerosing panencephalitis was made, hence the decision to hospitalize the patient.

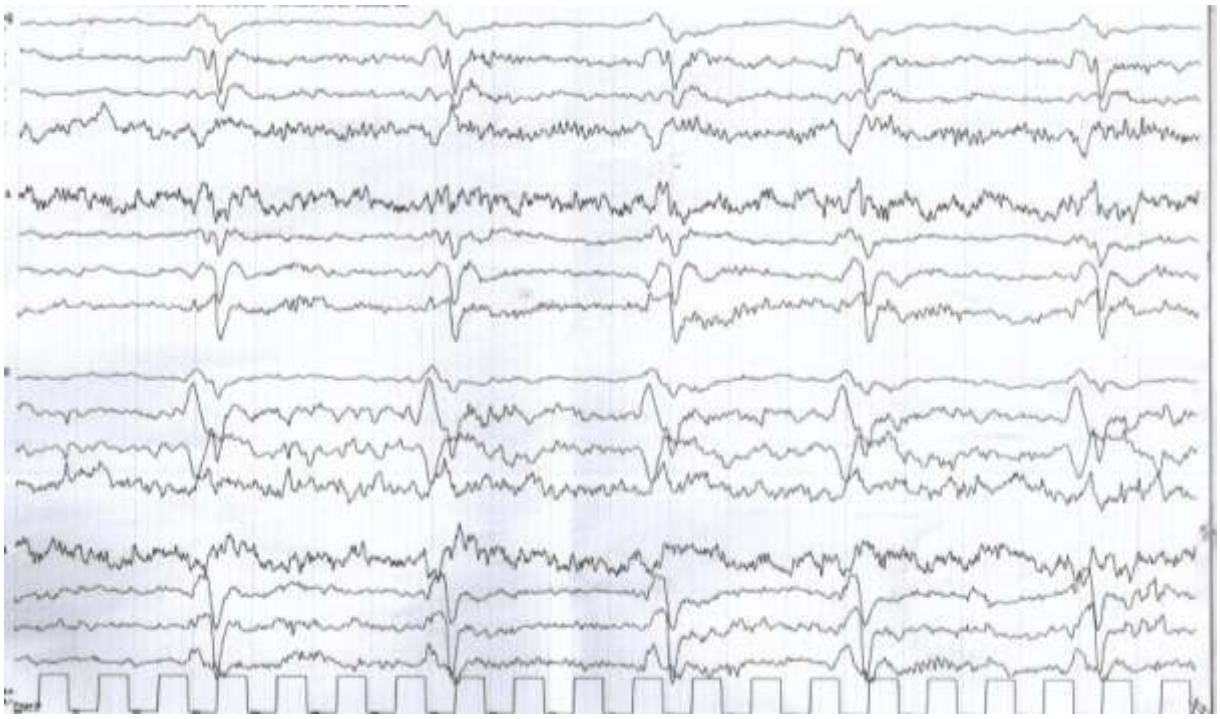

Figure: An EEG showing symmetrical, identical periodic burst high voltage discharges.

The workup was completed with blood collection and lumbar tap for cerebrospinal fluid analysis. The biochemistry and cytology of the CSF were normal. IgM anti-measles antibodies were negative in both blood and CSF, whereas the IgG antibodies were positive in the blood and CSF, and the CSF IgG / serum IgG ratio was 1.04.
Magnetic resonance imaging could not be done because the parents could afford to pay for it. The patient was put on carbamazepine and isoprinosine. Three days later the patient was discharged and was seen for a control after one month. An assessment three months after showed considerable regression of the myoclonic jerks.

DISCUSSION

In our patient, there was no past history of measles infection. Bonifas-Galup et al noted that in about a quarter of cases, no past history of measles infection is noted [11]. The absence of measles does not formally rule out the diagnosis of SSPE. SSPE in previously immunized child can be attributed to vaccine failure due to inadequate preservation of the vaccine or low seroconversion of the host, or, alternatively, to subclinical measles infection before the host was immunized [7,12]
Concerning the pathogenesis of SSPE, it is generally accepted that measles virus (MV) can reach the brain by infecting circulating lymphocytes or endothelial cells. Transneuronal or axonal spread can also be considered. Viral antigens are expressed and induce anti-MV immune response. The stable persistent state, results from the balance between viral replication and host immune response. The host-related factors is not clearly elucidated, it may be transient immunosuppresion caused by MV especially in an immunologically immature child; age, poor nutritional status, or concurrent infections may also contribute to inadequate immune response. The virus-related factor is the mutation in the MV which allows it to escape humoral immunity. MV isolated from patients with SSPE usually display mutations in the matrix (M) and/or fusion (F) genes. Hypermutations in the M gene are not lethal for the virus, which can still replicate and spread with slow migration. The wild MV undergoes these mutations during its stay in the host; shorter latest periods are associated with smaller number of mutations. The reason the virus becomes reactivated in some is unknown; alterations in immune or hormonal systems might be contributive [7].

There are four main stages of the disease; the first stage consists of intellectual deterioration and behavioral changes, with decreased school performance because of agnosia, apraxia, attention problems, irritability, and distractibility. In stage two we have then myoclonic jerks, incoordination, choreoathetosis and tremors. In stage three there are extrapyramidal, pyramidal dysfunctions, opisthotonus and in stage four prominent severe dementia become evident while in the terminal stage, there is progressive unresponsiveness, with increasing hypotonia and decerebrate rigidity, swallowing and respiratory difficulties with autonomic dysfunction [5, 8]. Clinically, the patient appeared to be at stage 2 according to the Jabbour stages, which are characterized predominantly by myoclonic jerks in addition to cognitive impairment [13]. The clinical approach in making this diagnosis was easy. Though being in a region where measles is still a public health problem, SSPE is a disease entity which is rare or may be under- diagnosed. It took three consultations and a second EEG interpretation, to arrive at the diagnosis.
Regarding the EEG findings, our patient's was characteristic of SSPE with symmetrical, identical and periodic burst high voltage discharges; a finding in about 98% of cases with SSPE in a study by Praveen-kumar et al [14]. Though the first and second EEGs were the same, the diagnosis was not made after the first EEG was done, because this is a rare pathology and there is need to know the clinical presentation before expecting EEG findings to be in favor.
A normal cerebral scan cannot rule out the diagnosis, because white matter changes which is the main radiologic finding, is difficult to see on CT scan [13]. Cortical and sub cortical atrophy has also been described but this was not present in our case. The gold standard for neuro imaging diagnosis is the magnetic resonance imaging, which shows panencephalitic lesions in the white and grey matter [13].
Laboratory diagnosis is based on the presence of intrathecal production of anti-measles antibodies and the CSF IgG /serum IgG index which is supposed to be above 0.75, and the presence of oligoclonal IgG bands [6]. In our case, the biochemistry and cytology of the CSF were normal. Anti-measles antibody IgM was negative in both blood and serum, while IgG was positive. Although the quantification of IgG antibodies was not done, the ratio of the optical densities in CSF and serum was above 0.75. On the whole, our patient presented with symptoms, EEG findings, IgG anti measles antibodies in the CSF, all consistent with SSPE.
Being a neurodegenerative disease, much is not expected regarding the prognosis. However it will be interesting for us to monitor this patient on carbamazepine. The patient was put on isoprinosine which has antiviral and immunomodulatory properties capable of slowing viral replication [7] and carbamazepine, which has been shown to produce a temporary, symptomatic improvement in myoclonus [10].
While on this treatment, there has been regression of the myoclonic jerks, but it is still early for us to assess the efficacy of this treatment. Follow-up is still

pursued because SSPE has a fatal course within one to three years [15].

CONCLUSION

SSPE even with its typical presentation can be difficult to be diagnosed because it is rare, under or misdiagnosed in our context. Typical EEG findings are supposed to be the basis of the diagnosis, alongside the presence of myoclonus, even in the absence of measles. SSPE should therefore be thought of, in a patient with cognitive impairment and myoclonus in our context where measles is not rare.

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