Case study

Movement disorder early in the presentation of two children with Subacute Sclerosing PanEncphalitis

Abstract.

Subacute sclerosing panencephalitis (SSPE) is a progressive degenerative disease caused by measles infection with overall poor prognosis in spite multiple modalities of treatment. The course of the disease is characterized by progressive neurological decline in the form of behavioral and personality changes followed by a stage of characteristic periodic myoclonic spasms followed by a stage of quadriplegia movement disorder and vegetative state and frequently early death. Here we report two cases with atypical presentation of early rather than late movement disorder during illness and the unusual association of central precocious puberty preceding the course of illness in one of the cases.

Keywords

SSPE: Subacute sclerosing panencephalitis**,** MRI: Magnetic resonance imaging, EEG: Electroencephalography, CNS: central nervous system, CSF: Cerebrospinal fluid, IFN-a: Interferons, CPP: central precious puberty, GnRH: Gonadotropin-releasing hormone, ER: Emergency Room**,** IVIG: Intravenous immune globulin, CD 90: Cluster of Differentiation 90, FH: Follicle-stimulating hormone, LSH: Luteinizing hormone, IRF-1: interferon regulatory factor-1, ACE: angiotensin converting enzyme, GTCS: Generalized Tonic-Clonic Seizures**,** CD20: Cluster of Differentiation 20.

Introduction.

Subacute sclerosing panencephalitis (SSPE) is a chronic, persistent encephalitis and invariably fatal degenerative disease secondary to a measles infection that causes severe demyelination of the CNS (1). It affects both gray matter and white matter, with very poor prognosis and high mortality rate, however, the exact pathogenesis is not clearly understood (2, 3). The initial presenting symptoms are progressive intellectual deterioration, psychomotor impairment, myoclonic jerks,

drop attacks, abnormal gait, abnormal movements, speech impairment, inability to walk or stand, seizures, dementia, visual disturbance, pyramidal and extra pyramidal signs (4, 5)

Regarding the vaccination, many genetic studies supported that measles virus vaccination does not cause SSPE (6-8). It protects against SSPE and (9), the administration of the vaccination does not alter the course of SSPE or trigger it in an individual who already developed the disease (10).

The diagnose of SSPE requires criteria including evidence of increased measles antibodies in CSF or measles virus in brain biopsy (11). Regarding the clinical Stages, it has been divided to 4 stages(12, 13); stage one, mainly behavioral, cognitive and personality changes; stage two, myoclonic spasms, language difficulties and motor signs; stage three, loss of ambulation, extrapyramidal symptoms with decrease responsiveness; and stage four, vegetative state with no myoclonus.

For treatment, Isoprinosine was the first drug reported to be effective. It helped in stabilizing the course of SSPE(14-16) due to its immuno-modulatory effects. The drug is beneficial in 30–34% of the cases, but it is ineffective in the rapid progressing stage of the disease (11, 17, 18). Interferon (IFN-a) was used with possible efficacy (19, 20), but lately it was found to be ineffective in a randomized control trial (11). Furthermore, Ribavirin showed benefit in treating SSPE in some studies (21, 22).

SSPE incidence may differ geographically from one area to another, and it generally declined since the introduction of measles vaccine (23). Overall, the highest incidence of SSPE relative to the rate of infection was found in the Middle East, the rate was 360⁄100 000 in people infected before 1 year of age (24), so the annual incidence is 2.4 per million population (25). There are few reports on SSPE from Saudi Arabia. Here we report two non-Saudi patients with SSPE seen at King Abdul-Aziz Medical City (KAMC) in Riyadh over 15 years. The course of the illness was rapid progression with unusual extra pyramidal symptoms early during the course of the illness.

Case 1.

8 years old Filipino girl with history of measles infection at age of 6 months was followed at KAMC because of central precious puberty (CPP)under treatment with

Gonadotropin-releasing hormone analogue (GnRH analogue) injection once/month for 10 months. Brain MRI was done outside which was unremarkable except for small enhancing region that indicates micro adenomatous changes in the pituitary gland.

She started having abnormal day dreaming, frightening attacks, bed wetting, hyperactivity, and lack of concentration, so she presented to another hospital and was started on Carbamazepine then lamotrigine was added due to lack of improvement.

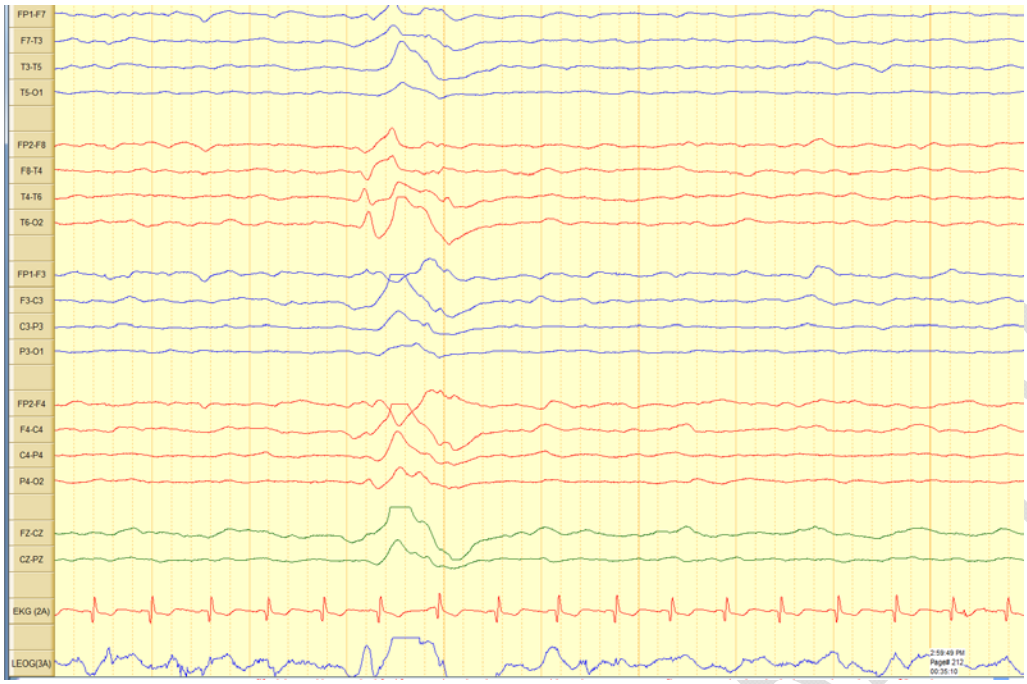
During the next two months she developed unsteady gait, dysarthria, head nodding, chorea like movements, forgetfulness and difficulty in understanding commands and she was away from school during this two-month prior. Two weeks prior to her presentation to KAMC she developed myoclonic jerks.

When she presented to our ER, she was bedridden, responding to her name by turning her head, opening her eyes spontaneously but poorly following or fixing, continuously having myoclonic jerk of the whole body that disappear while sleeping, with normal tone, brisk reflexes and reactive pupils.

Brain MRI showed high T2 signal bilateral paratio-occipital and peri trigonal regions with contrast enhancement. The EEG showed slow background with bursts of high amplitude semi periodic slow waves with sharp activity (figure 1). Based on a very high CSF and serum measles IgG antibodies titters the diagnosis of SSPE was confirmed. She was treated with Isoprinosine orally with escalating dose to 1.5 gram twice daily (83 mg/kg/day). Also, she received a course of IVIG with total dose of 2 gram/kg. For seizures, she was on Phenobarbital and valproic acid and for choreoathetosis she was treated with haloperidol. Afterwards, she became more awake and had less chore athetotic and myoclonic movements. Upon discharge and based on her condition she classified to be more on stage 3 of the disease.

After 5 months family documented that she is a little bit improved in form of being more following and fixing by her eyes and less myoclonic jerks were observed.

Fourteen months after discharge she was in a vegetative state with spastic quadriplegia and was wheelchair bound (stage 4). Afterwards she was lost to follow up.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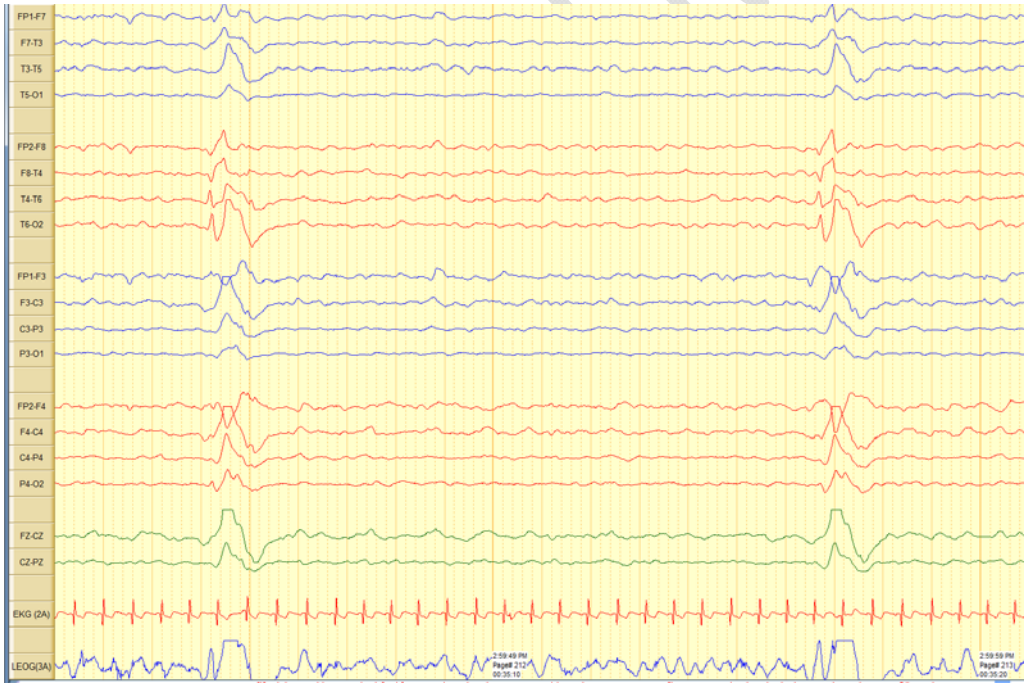
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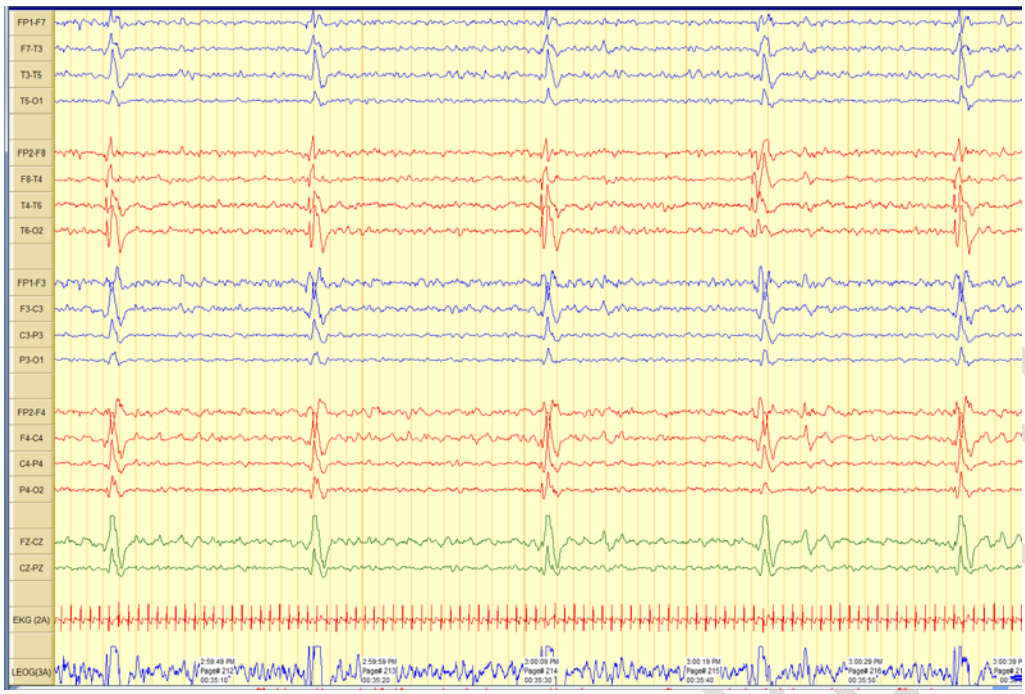

Figure 1: The EEG shows slow background with bursts of high amplitude semi periodic slow waves with sharp activity. Sensitivity is 30 µv/mm and paper speed are 30 mm/sec(A), 15 mm/sec(B), and 5 mm/sec(C)

Case 2.

A 10 years old Syrian boy with history of measles infection at age of 1 year old presented with a recent history of 3 times generalized convulsions, behavioural and personality changes over 3-week period. This progressed rapidly to the point he lost ambulation, speech and eye contact.

In our hospital, he was non-verbal with poor eye contact. He moved his limbs freely to stimulation but did not reach for offered objects. Reflexes were intact. He was started on Acyclovir, Vancomycin, Ceftriaxone and phenytoin.
Initial EEG showed diffuse slowing and the brain MRI was normal. He received a 5-day pulse methylprednsone followed by a course of IVIG.

Seventeen days after admission he developed chorea like movements involving mainly oro-bucal area, head and limbs. He was started on Risperidone with fair response.

One week after the IVIG course and based on provisional diagnosis of autoimmune encephalitis he received rituximab 500mg/m2/day over 3 days. Clinically some improvement was noticed after each dose of rituximab in the form of having fair eye contact, responding to name, producing sounds and ambulating with assistance. Afterwards the rituximab was not given anymore because of CD90 declining to zero.

Thirty-six days after admission, he started having sudden body jerks that became periodic at about 9-10 seconds interval. The EEG at that time showed diffuse slowing with paroxysmal attenuation and sharp waves discharges seen on the bilateral frontal areas. Periodic high amplitude slow wave activity occurred almost every 9 seconds associated with whole body myoclonic spasms.

The diagnosis of SSPE was confirmed with EEG findings and high CSF and serum measles IgG titters. The patient received Ribavirin escalating dose to 40 mg/kg/day and vitamin A dose of 40,000 unites every week via nasogastric tube.
He continued to have myoclonic spasms despite of multiple drugs used including phenytoin and levetiracetam followed by Carbamazepine and Valproic acid. He underwent a gastrostomy tube insertion; he showed a significant improvement with physiotherapy and occupational therapy, he could walk with assistant, so he was discharged home. Three months later, he was admitted again because of persistent fever, and increase the frequency of seizures, so infectious diseases were involved, and all the investigation came back to be negative, the patient diagnosed to have central hyperthermia, and the anti-epileptic drugs were adjusted, then discharged home. Afterwards, he continued to decline in his activity and responsiveness to vegetative state and he expired one year later.

Discussion.

These cases are the only cases reported in our institution over the past 15 years. Both are non-Saudi patients coming from countries where massive vaccination against measles is not routinely achieved. The diagnosis was suspected after the periodic myoclonic spasms appeared that led to the final diagnosis. Both cases have movement disorder early in the course of illness before the myoclonic spasms appeared. This feature is rarely reported in the literature (26). According to staging systems the myoclonic stage follows the behavioral and personality changes then the extrapyramidal movement disorder and spasticity follows (12). Neuro-pathological findings indicated initial effect on the occipital areas followed by anterior areas of the cortex, while subcortical structures like basal ganglia,

brainstem and spinal cord are affected at later stage(27). We hypothesize that in these two patients the involvement of deep grey matter occurs early. In the first patient, the choreoathetosis was so remarkable at presentation that it required treatment with Haloperidol. This could reflect the early involvement of deep grey matter as well. In both cases the MRI findings are not remarkable. In the first case, white matter changes were minimal while brain atrophy was remarkable. Likewise, the second case had normal MRI to be followed later with brain atrophy and no white matter changes. These neuro-radiological findings may support our hypothesis of involving grey matter including deep grey matter early in the course. Only 3/76 cases showed involvement of basal ganglia on MRI during all were in stage 3 of SSPE (28).

The presence of central precocious puberty (CPP) in the first patient prior to cognitive decline is intriguing. The diagnosis of CPP was done 10 months prior to SSPE presentation and she was on GnRHanalogue during the whole time. The presence of micro adenomatous changes associated with precocious puberty in young girls is considered an incidental finding that may disappear on follow up studies. Intra-glandular micro adenomatous changes are MRI features of contrast enhancement that is not proven on microscopic level (29). The relation of CPP to SSPE in this case is unclear. From the pathophysiology point, the puberty depends on increase secretion of GnRH from hypothalamus that ultimately induce FH and LSH from pituitary gland, so leading to maturation of gonads and appearing of secondary sexual characteristic. There are two types either central or peripheral. If the cause can be traced to be from hypothalamus or pituitary gland, it named central(30, 31), and it is within the neuronal and glial network. The measles virus affects the CNS either by direct infection of endothelial cells or in infected leukocytes, usually neurons with oligo-dendrocytes are dominantly the one will be affected (32). In the terminal not in early stages of the disease, it affects the hypothalamus resulting in hypothalamic failure which manifests as intermittent hyperthermia, irregular breathing, blood pressure abnormalities, and abnormal pulse (33) but in early stages it affects the occipital areas, spreading to the anterior portion of the cortex. Then other parts will be involved like subcortical structures, brain stem, and spinal cord. Ultimately no case was reported before describing CPP preceding SSPE symptoms. Although, the association between the two conditions is likely to be coincidental it is also likely that they can be related with

early start of the disease with hypothalamic/pituitary involvement by the viral infection.

The CPP was linked to LIN28B**,** LIN28A (34-40)**,** KISS1**,** and KISS1R (41-43)mutations, but SSPE was more linked to functional polymorphisms of MxA, interleukin(IL)-4 and interferon regulatory factor-1 (IRF-1) genes especially in Japan and angiotensin converting enzyme (ACE) gene polymorphism more in Turkey (44). Thus, the possibility of genetic predisposition in the first case for both conditions is another possibility but never been proven as the current advanced genetic sequencing was not available then.

Another atypical presentation is also seen in the second case where it started with fever, vomiting and GTCS one week prior to behavioral changes. Similar case was reported from Turkey with GTCS one month prior to other symptoms (45). Focal or generalize seizures as first presentation to SSPE was report in 8-17% of cases(4, 45-50). Focal EEG changes were recorded in our patient followed by other typical findings of periodic discharges and progressive burst suppression. Similar case was reported in a Japanese patient (51).

The second case showed some response to rituximab injection in form of being responding to his name by turning his head and making sounds but unfortunately the effect was transient despite biomarker feature of decreased CD20-expressing B cells. This finding was report in case treated with this medication (52).

In conclusion: SSPE is a neurologically devastating disease with characteristic clinical and EEG features but atypical presentation with extrapyramidal movement disorder can be early rather than late during the disease.

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