

Movement disorder early in the presentation of two children with Subacute Sclerosing Pan-Encephalitis

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, 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- α : 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- α) 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 precocious 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.

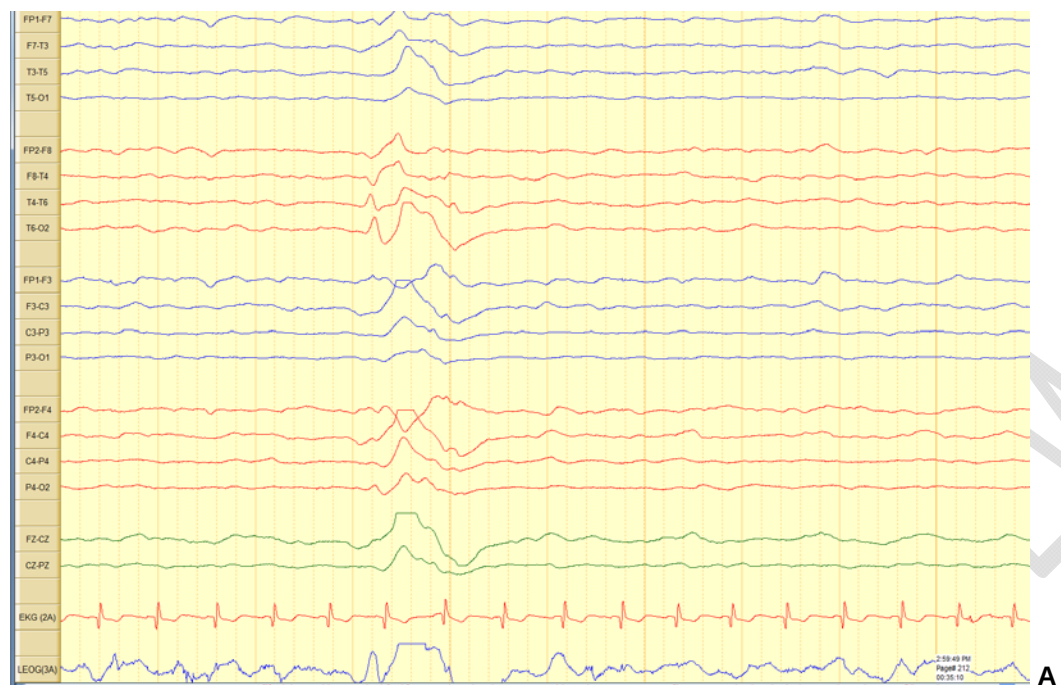
During the next two months she developed unsteady gait, dysarthria, head nodding, chorea like movements, forgetfulness and difficulty in understanding commands and she was away from school during this two-month prior. Two weeks prior to her presentation to KAMC she developed myoclonic jerks.

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.

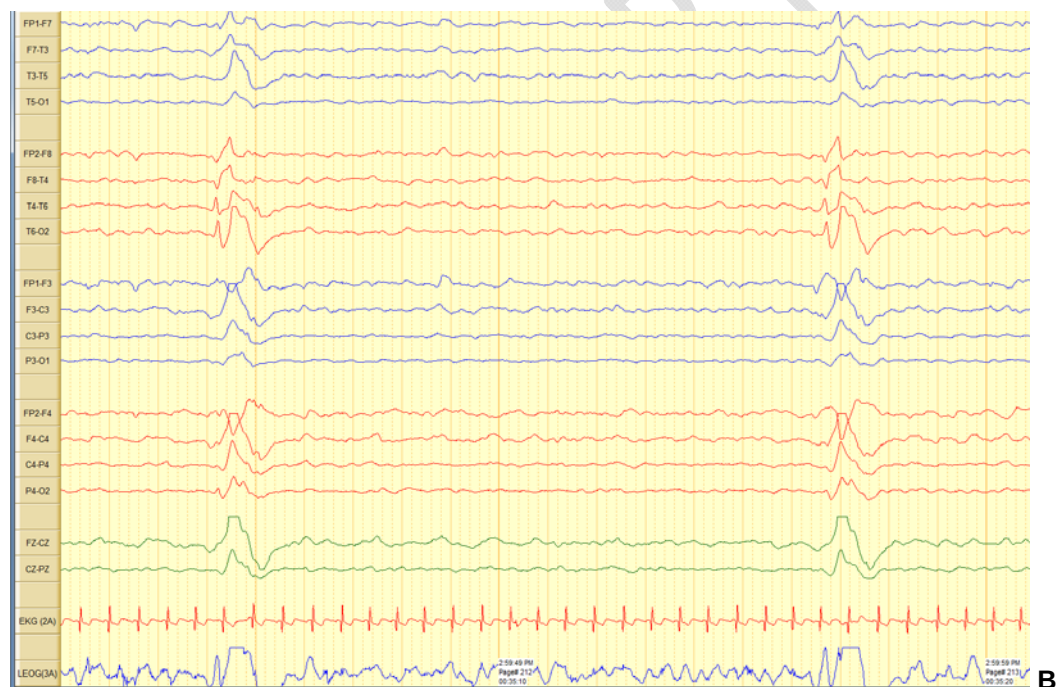
Brain MRI showed high T2 signal bilateral parieto-occipital and peri trigonal regions with contrast enhancement. The EEG showed slow background with bursts of high amplitude semi periodic slow waves with sharp activity (figure 1). Lumber puncture was done within the first week, and the CSF data including: WBC, protein, glucose was all normal, but the CSF measles IgG antibody was high, so based on a very high CSF and serum measles IgG antibodies titers 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 choreoathetosis 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.



A



B



Figure 1: The EEG shows slow background with bursts of high amplitude semi periodic slow waves with sharp activity. Sensitivity is 30 μ v/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. Patient received in ER, lumbar puncture done and he was admitted under our care. He was started on Acyclovir, Vancomycin, Ceftriaxone and phenytoin, the initial result of CSF was negative including WBC, protein, glucose, and culture, so we discontinue the antibiotics, and while waiting for the results of the auto-immune encephalitis markers we treated him as an autoimmune one.

Initial EEG showed diffuse slowing and the brain MRI was normal (figure 2). He received a 5-day pulse Methylprednisolone followed by a course of IVIG, the initial CSf results were all normal, so we consider auto-immune encephalitis, and we treated him based on that.

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 CD20 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, so lumbar puncture was repeated and we send for anti-measles IgG titre anti-body, and we check the serum level too, at that time the results of CSF auto-immune encephalitis received to be negative.

The diagnosis of SSPE was confirmed with EEG findings and high CSF and serum measles IgG titers. 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 physicians 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.

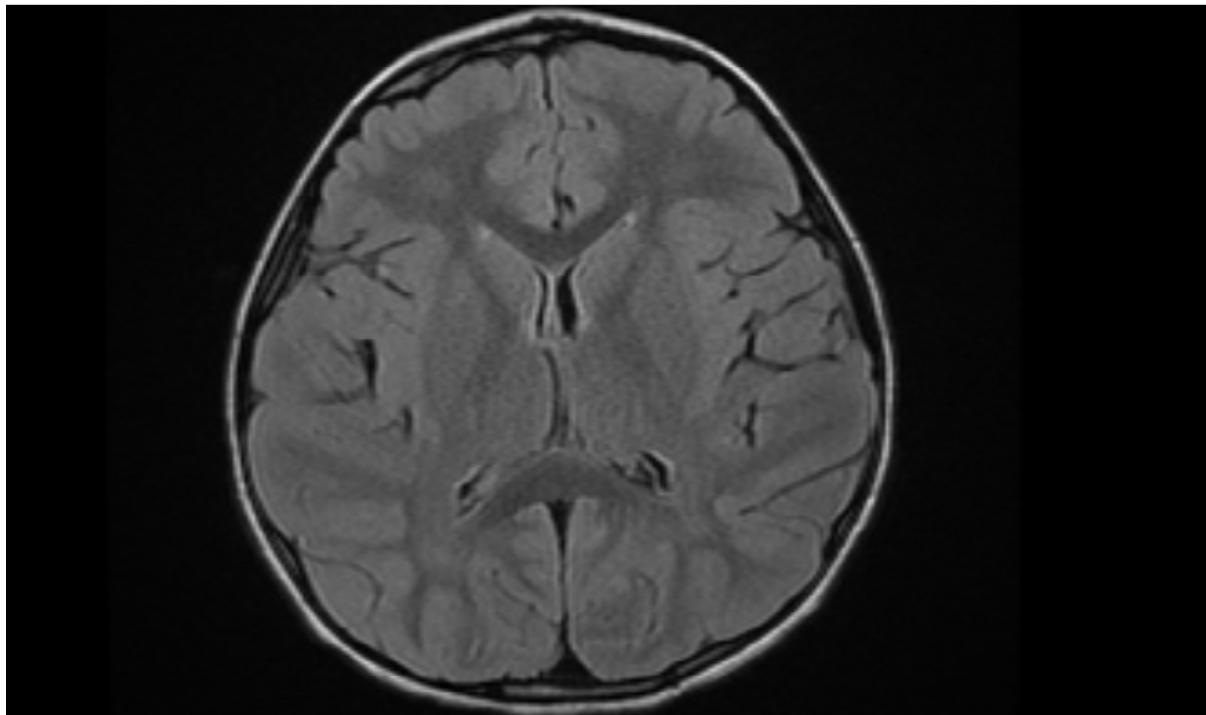


Figure 2A: axial T2 Flair

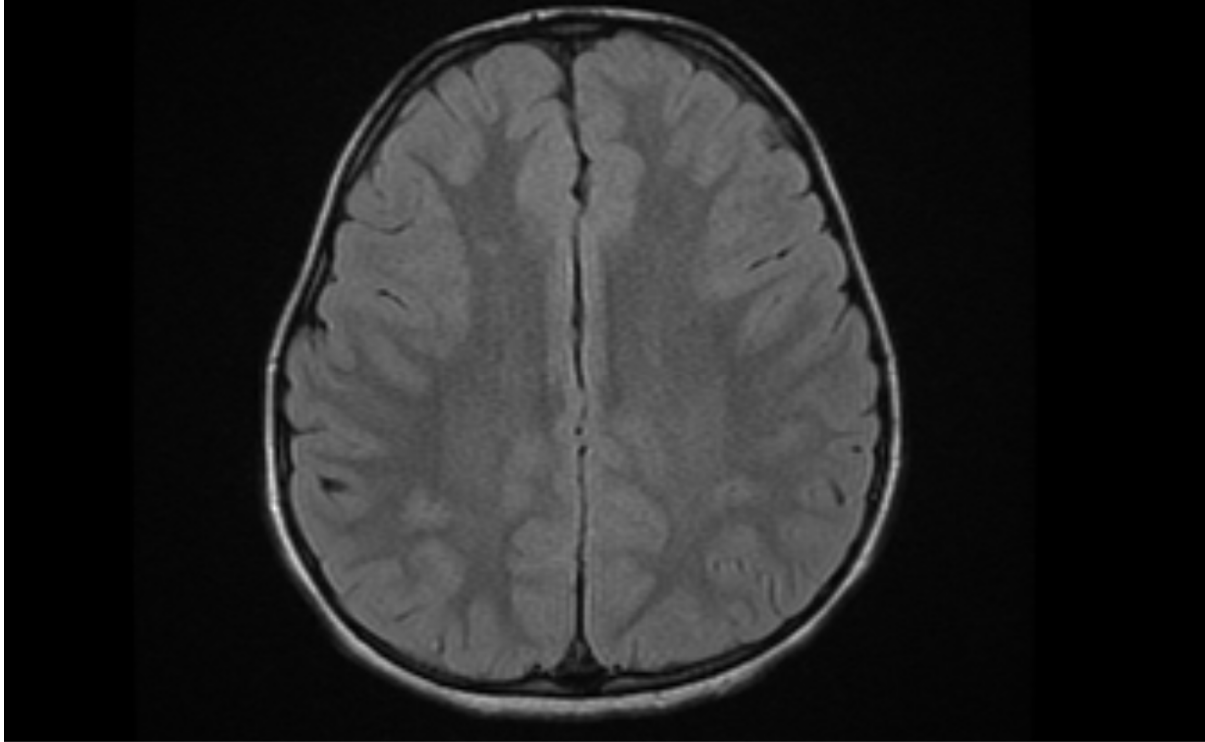


Figure 2B: Axial T2 Flair

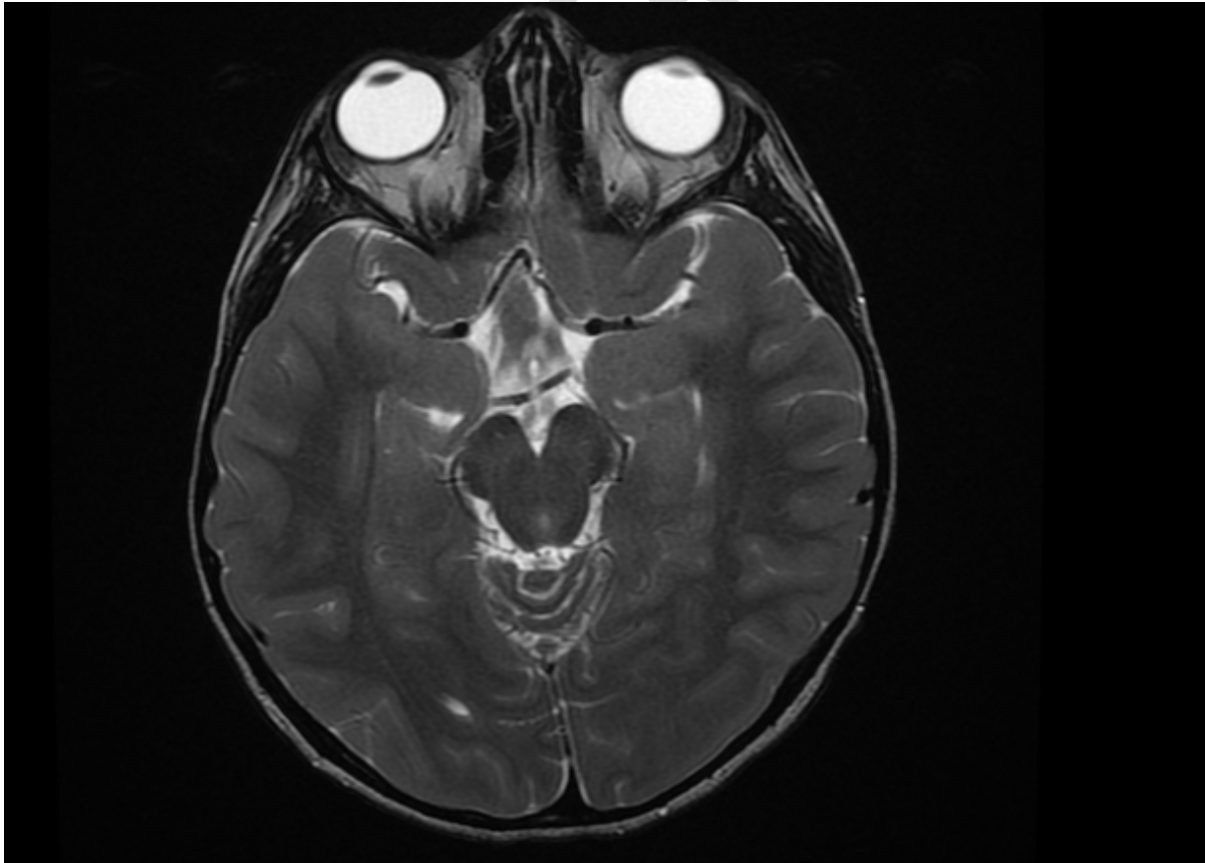


Figure 2C: Axial T2

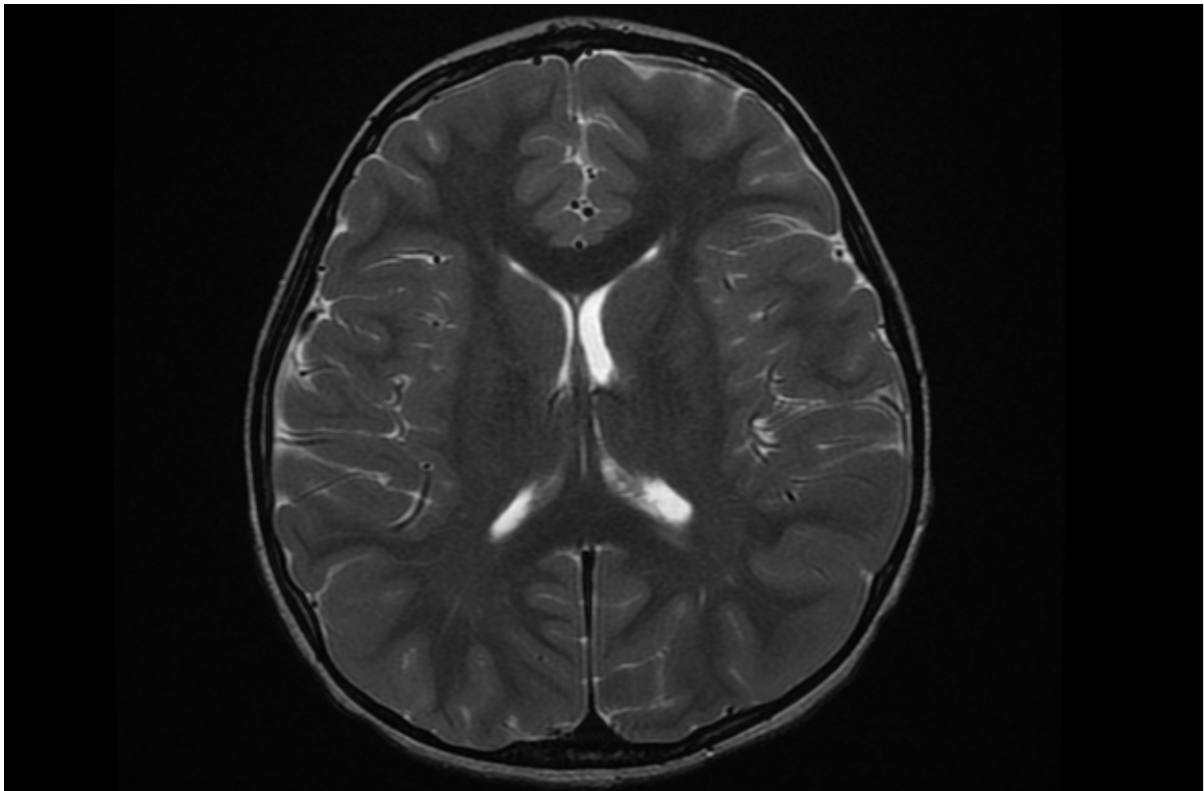


Figure 2D: Axial T2

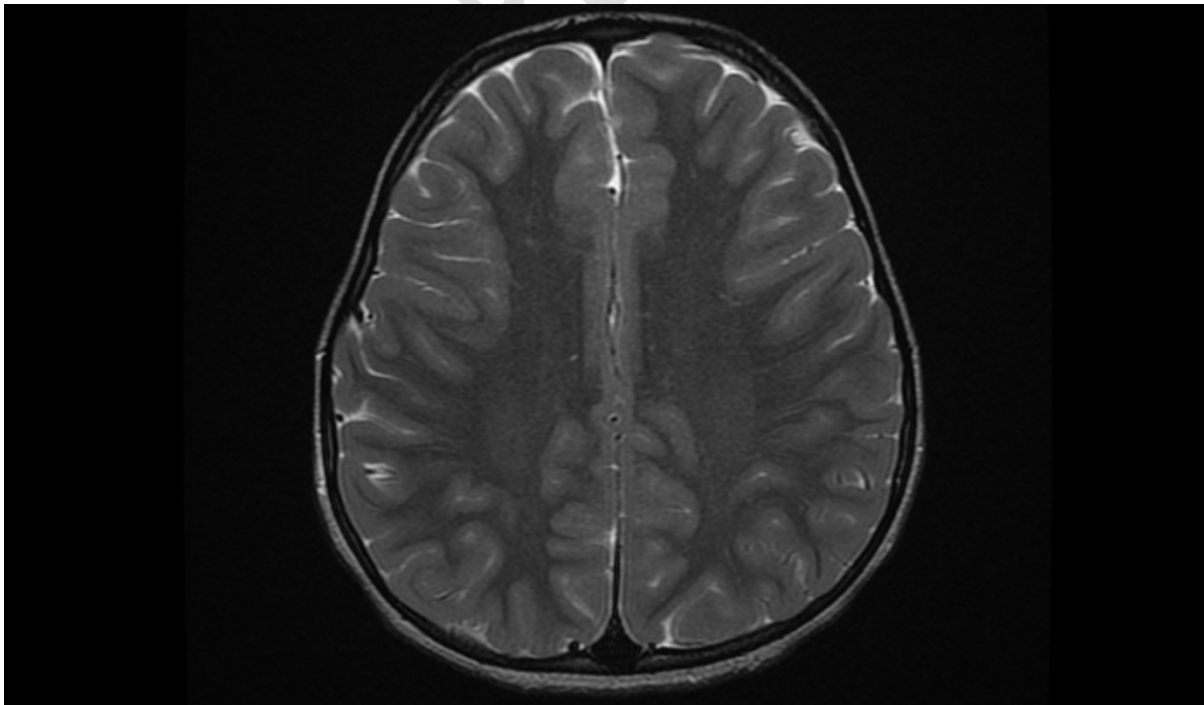


Figure 2E: Axial T2

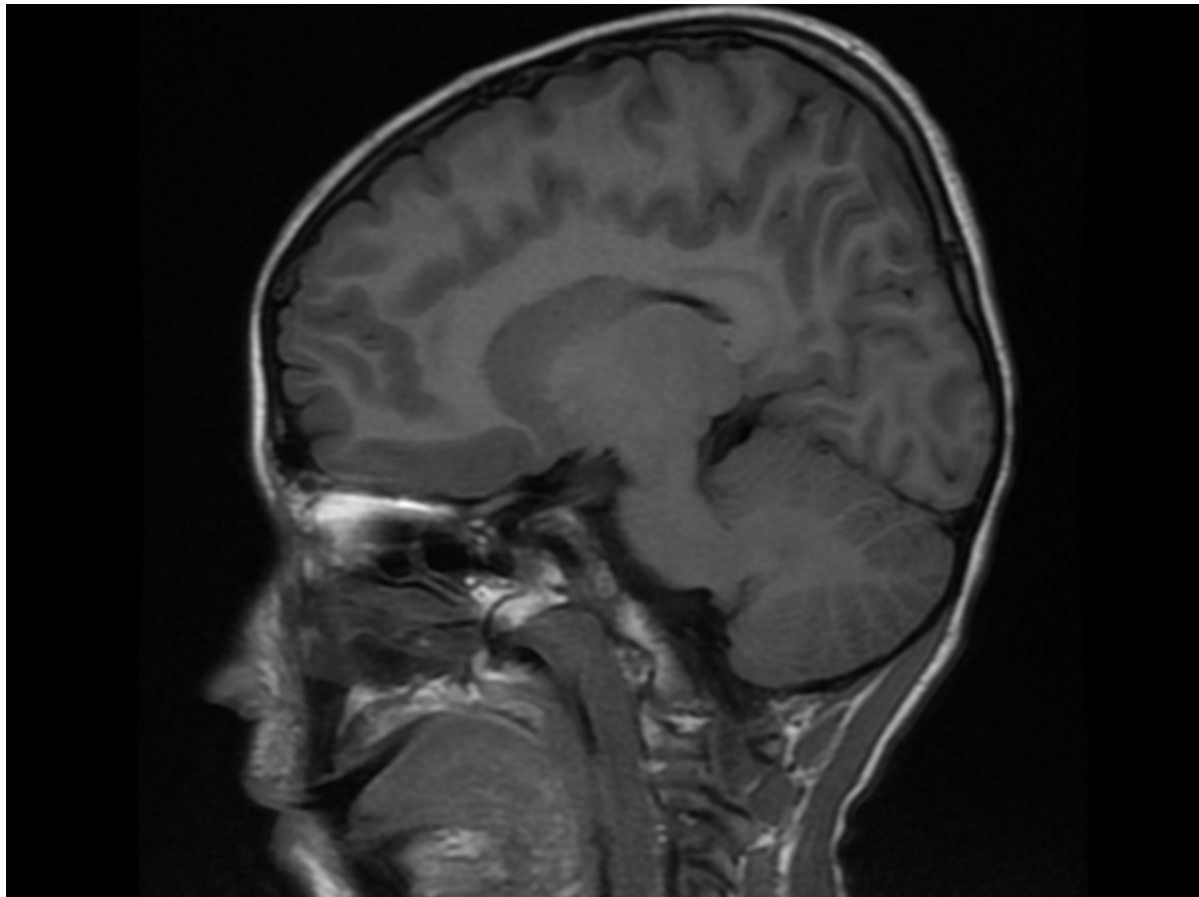


Figure 2F: Sagittal T1

Figure 2 Brain MRI showed normal study.

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 were not similar. In fact, the first case, her brain MRI showed high T2 signal

bilateral parieto-occipital and peri trigonal regions with contrast enhancement with remarkable brain atrophy. 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 GnRH-analogue 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, and 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 **considered** 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, **few cases were reported worldwide, two cases were presented to our institute within 15 years, with atypical symptoms** so, atypical presentation with extrapyramidal movement disorder can be early rather than late during the disease.

Consent Disclaimer:

As per international standard or university standard, parent's consent has been collected and preserved by the authors.

References.

1. Gutierrez J, Issacson RS, Koppel BS. Subacute sclerosing panencephalitis: an update. *Developmental Medicine & Child Neurology*. 2010;52(10):901-7.
2. Weissbrich B, Schneider-Schaulies J, Meulen Vt. Measles and its neurological complications. *NEUROLOGICAL DISEASE AND THERAPY*. 2004;60:401-30.
3. Reuter D, Schneider-Schaulies J. Measles virus infection of the CNS: human disease, animal models, and approaches to therapy. *Medical microbiology and immunology*. 2010;199(3):261-71.
4. Prashanth L, Taly A, Sinha S, Ravi V. Subacute sclerosing panencephalitis (SSPE): an insight into the diagnostic errors from a tertiary care university hospital. *Journal of child neurology*. 2007;22(6):683-8.
5. Salehi HR, Delgado E, Wolf SM, McGoldrick PE, Moshé SL. Subacute sclerosing panencephalitis with atypical features. *Pediatric neurology*. 2005;33(4):280-2.
6. Jin L, Beard S, Hunjan R, Brown D, Miller E. Characterization of measles virus strains causing SSPE: a study of 11 cases. *Journal of neurovirology*. 2002;8(4):335-44.
7. Halsey NA, Modlin JF, Jabbour J, Dubey L, Eddins DL, Ludwig DD. Risk factors in subacute sclerosing panencephalitis: a case-control study. *American Journal of Epidemiology*. 1980;111(4):415-24.
8. Zilber N, Rannon L, Alter M, Kahana E. Measles, measles vaccination, and risk of subacute sclerosing panencephalitis (SSPE). *Neurology*. 1983;33(12):1558-64.
9. Organization WH. Global Advisory Committee on Vaccine Safety, 1-2 December 2005= Comité consultatif mondial de la sécurité vaccinale, 1er-2 décembre 2005. *Wkly Epidemiol Rec*. 2006;81(02):15-9.
10. Campbell H, Andrews N, Brown K, Miller E. Review of the effect of measles vaccination on the epidemiology of SSPE. *International journal of epidemiology*. 2007;36(6):1334-48.
11. Gascon GG. Randomized treatment study of inosiplex versus combined inosiplex and intraventricular interferon- α in subacute sclerosing panencephalitis (SSPE): International multicenter study. *Journal of child neurology*. 2003;18(12):819-27.
12. Jabbour J, Garcia JH, Lemmi H, Ragland J, Duenas DA, Sever JL. Subacute sclerosing panencephalitis: a multidisciplinary study of eight cases. *Jama*. 1969;207(12):2248-54.
13. Risk WS, Haddad FS. The variable natural history of subacute sclerosing panencephalitis: a study of 118 cases from the Middle East. *Archives of neurology*. 1979;36(10):610-4.
14. Streletz L, Cracco J. The effect of isoprinosine in subacute sclerosing panencephalitis (SSPE). *Annals of neurology*. 1977;1(2):183-4.
15. Huttenlocher PR, Mattson RH. Isoprinosine in subacute sclerosing panencephalitis. *Neurology*. 1979;29(6):763-.
16. Jones C, Huttenlocher P, Dyken P, Jabbour J, Maxwell K. Inosiplex therapy in subacute sclerosing panencephalitis: a multicentre, non-randomised study in 98 patients. *The Lancet*. 1982;319(8280):1034-7.
17. Fukuyama Y, Nihei K, Matsumoto S, Ebina T, Kamoshita S, Sato T, et al. Clinical effects of MND-19 (Inosiplex) on subacute sclerosing panencephalitis:—A multi-institutional collaborative study—. *Brain and Development*. 1987;9(3):270-82.
18. Dyken PR, Swift A, Durant RH. Long-term follow-up of patients with subacute sclerosing panencephalitis treated with inosiplex. *Annals of neurology*. 1982;11(4):359-64.
19. Nakagawa M, Michihata T, Yoshioka H, Sawada T, Kusunoki T, Kishida T. Intrathecal administration of human leukocyte interferon to a patient with subacute sclerosing panencephalitis. *Acta Paediatrica*. 1985;74(2):309-10.
20. Panitch H, Gomez-Plascencia J, Norris F, Cantell K, Smith R. Subacute sclerosing panencephalitis: remission after treatment with intraventricular interferon. *Neurology*. 1986;36(4):562-6.
21. Tomoda A, Nomura K, Shiraishi S, Hamada A, Ohmura T, Hosoya M, et al. Trial of intraventricular ribavirin therapy for subacute sclerosing panencephalitis in Japan. *Brain and Development*. 2003;25(7):514-7.

22. Hosoya M, Mori S, Tomoda A, Mori K, Sawaishi Y, Kimura H, et al. Pharmacokinetics and effects of ribavirin following intraventricular administration for treatment of subacute sclerosing panencephalitis. *Antimicrobial agents and chemotherapy*. 2004;48(12):4631-5.
23. Saha V, John TJ, Mukundan P, Gnanamuthu C, Prabhakar S, Arjundas G, et al. High incidence of subacute sclerosing panencephalitis in South India. *Epidemiology & Infection*. 1990;104(1):151-6.
24. Zilber N, Kahana E. Environmental risk factors for subacute sclerosing panencephalitis (SSPE). *Acta neurologica scandinavica*. 1998;98(1):49-54.
25. Radhakrishnan K, Thacker A, Maloo J, Gerryo S, Mousa M. Descriptive epidemiology of some rare neurological diseases in Benghazi, Libya. *Neuroepidemiology*. 1988;7(3):159-64.
26. Bojinova VS, Dimova PS, Belopitova LD, Mihailov AS, Gatcheva NL, Mihneva ZG, et al. Clinical and epidemiological characteristics of subacute sclerosing panencephalitis in Bulgaria during the past 25 years (1978–2002). *European Journal of Paediatric Neurology*. 2004;8(2):89-94.
27. Ohya T, Martinez AJ, Jabbour J, Lemmi H, Duenas DA. Subacute sclerosing panencephalitis correlation of clinical, neurophysiologic and neuropathologic findings. *Neurology*. 1974;24(3):211-.
28. Cece H, Tokay L, Yildiz S, Karakas O, Karakas E, Iscan A. Epidemiological findings and clinical and magnetic resonance presentations in subacute sclerosing panencephalitis. *Journal of International Medical Research*. 2011;39(2):594-602.
29. Pedicelli S, Alessio P, Scirè G, Cappa M, Cianfarani S. Routine screening by brain magnetic resonance imaging is not indicated in every girl with onset of puberty between the ages of 6 and 8 years. *The Journal of Clinical Endocrinology & Metabolism*. 2014;99(12):4455-61.
30. GARDNER DGG. *Basic & clinical endocrinology*: Lange Medical Books; 2003.
31. Dorland WAN. *Dorland's medical dictionary*: Saunders; 1968.
32. Cosby S, Duprex W, Hamill L, Ludlow M, McQuaid S. Approaches in the understanding of morbillivirus neurovirulence. *Journal of NeuroVirology*. 2002;8.
33. Zagami A, Lethlean A. Chorioretinitis as a possible very early manifestation of subacute sclerosing panencephalitis. *Internal Medicine Journal*. 1991;21(3):350-2.
34. Perry J, Stolk L, Franceschini N, Lunetta K, Zhai G, McArdle P, et al. van MJ, Nalls MA, Rivadeneira F, Shuldiner AR, Singleton A, Soranzo N, Tanaka T, Visser JA, Weedon MN, Wilson SG, Zhuang V, Streeten EA, Harris TB, Murray A, Spector TD, Demerath EW, Uitterlinden AG, Murabito JM. Meta-analysis of genome-wide association data identifies two loci influencing age at menarche. *Nat Genet*. 2009;41:648-50.
35. Ong KK, Elks CE, Li S, Zhao JH, Luan Ja, Andersen LB, et al. Genetic variation in LIN28B is associated with the timing of puberty. *Nature genetics*. 2009;41(6):729-33.
36. He C, Kraft P, Chen C, Buring JE, Paré G, Hankinson SE, et al. Genome-wide association studies identify loci associated with age at menarche and age at natural menopause. *Nature genetics*. 2009;41(6):724-8.
37. Sulem P, Gudbjartsson DF, Rafnar T, Holm H, Olafsdottir EJ, Olafsdottir GH, et al. Genome-wide association study identifies sequence variants on 6q21 associated with age at menarche. *Nature genetics*. 2009;41(6):734-8.
38. Tommiska J, Wehkalampi K, Vaaralahti K, Laitinen E-M, Raivio T, Dunkel L. LIN28B in constitutional delay of growth and puberty. *The Journal of Clinical Endocrinology & Metabolism*. 2010;95(6):3063-6.
39. Moss EG, Lee RC, Ambros V. The cold shock domain protein LIN-28 controls developmental timing in *C. elegans* and is regulated by the *lin-4* RNA. *Cell*. 1997;88(5):637-46.
40. Zhu H, Shah S, Shyh-Chang N, Shinoda G, Einhorn WS, Viswanathan SR, et al. Lin28a transgenic mice manifest size and puberty phenotypes identified in human genetic association studies. *Nature genetics*. 2010;42(7):626-30.
41. Teles MG, Bianco SD, Brito VN, Trarbach EB, Kuohung W, Xu S, et al. A GPR54-activating mutation in a patient with central precocious puberty. *New England Journal of Medicine*. 2008;358(7):709-15.
42. Silveira LG, Noel S, Silveira-Neto A, Abreu A, Brito V, Santos M, et al. Mutations of the KISS1 gene in disorders of puberty. *The Journal of Clinical Endocrinology & Metabolism*. 2010;95(5):2276-80.
43. Luan X, Yu H, Wei X, Zhou Y, Wang W, Li P, et al. GPR54 polymorphisms in Chinese girls with central precocious puberty. *Neuroendocrinology*. 2007;86(2):77.
44. Kusuhara K, Torisu H, Kira R, Hara T. Host genetic factors for the development of SSPE. *Nihon rinsho Japanese journal of clinical medicine*. 2007;65(8):1467-74.

45. Tuncel D, Ozbek AE, Demirpolat G, Karabiber H. Subacute sclerosing panencephalitis with generalized seizure as a first symptom: a case report. *Japanese journal of infectious diseases*. 2006;59(5):317.
46. Kissani N, Ouazzani R, Belaidi H, Ouahabi H, Chkili T. Epileptic seizures and epilepsy in subacute sclerosing panencephalitis (report of 30 cases. *Neurophysiologie clinique= Clinical neurophysiology*. 2001;31(6):398-405.
47. Öztürk A, Gürses C, Baykan B, Gökyiğit A, Eraksoy M. Subacute sclerosing panencephalitis: clinical and magnetic resonance imaging evaluation of 36 patients. *Journal of child neurology*. 2002;17(1):25-9.
48. Demir E, Aksoy A, Anlar B, Sonmez F. Atypical presentations of SSPE: a clinical study in four cases. *TURKISH JOURNAL OF PEDIATRICS*. 2007;49(3):295.
49. Demirbilek V, Benbir G, Cokar O, Yalcin D, Bulut H, Dervent A. Tonic seizures in subacute sclerosing panencephalitis: a video-illustration of two cases. *Epileptic disorders*. 2005;7(3):221-5.
50. Dimova PS, Bojinova VS. Case of subacute sclerosing panencephalitis with atypical absences and myoclonic-atonic seizures as a first symptom. *Journal of child neurology*. 2004;19(7):548-52.
51. Kubota T, Okumura A, Takenaka J, Ishiguro Y, Takahashi H, Ueda N, et al. A case of subacute sclerosing panencephalitis preceded by epileptic seizures: evolutionary EEG changes. *Brain and Development*. 2003;25(4):279-82.
52. Titomanlio L, Soyah N, Guerin V, Delanoe C, Sterkers G, Evrard P, et al. Rituximab in subacute sclerosing panencephalitis. *European Journal of Paediatric Neurology*. 2007;11(1):43-5.