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Tremor and Other Hyperkinetic Movements

Case reports

Subacute Sclerosing Panencephalitis Causing Rapidly Progressive Dementia and Myoclonic Jerks in a Sexagenarian Woman

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Abstract

Background: Subacute sclerosing panencephalitis (SSPE) is a disease of childhood and adolescence, but can affect adults. Rapidly progressive cognitive decline, seizures including myoclonic jerks, spasticity, ataxia, visual disturbances, and incontinence are typical manifestations.

Case report: A 62-year-old woman who presented with rapidly progressive dementia and myoclonus was diagnosed with SSPE. There was resolution of the movement disorder with clonazepam and valproic acid treatment and some amelioration of cognitive decline after 3 months of therapy with interferon alfa and isoprinosine.

Discussion: With the recent rise in measles cases worldwide, any increased incidence of SSPE would require vigilance for early interventions.

Keywords: Subacute sclerosing panencephalitis, myoclonic jerks, dementia, measles, isoprinosine, vaccination.

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Introduction

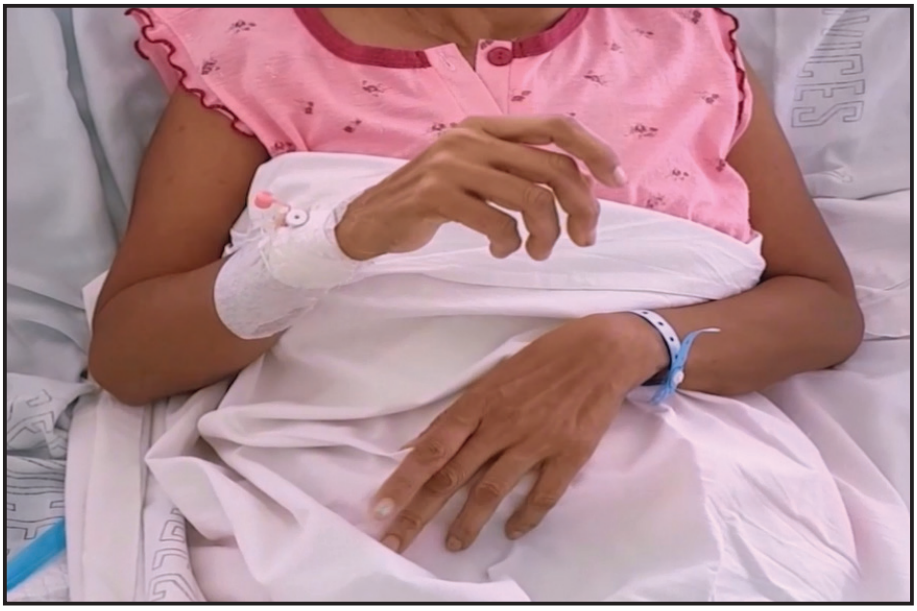
Subacute sclerosing panencephalitis (SSPE) is a progressive neurological disorder of childhood and early adolescence that is caused by persistent mutant measles virus genomes producing neurodegeneration, inflammation, and demyelination of the central nervous system (CNS). The disease is rarely reported among older people. It has a gradually progressive course that can lead to death within 1–3 years. The initial symptoms are usually subtle and include mild intellectual deterioration and behavioral changes that can progress to disturbances in motor function and development of myoclonic jerks, visual disturbances with pyramidal and extrapyramidal signs. Patients can also develop ataxia, dystonia, and dyskinesia. Generalized tonic–clonic seizures and partial seizures may also occur.[1–4]

We report a case illustrating rapidly progressive dementia, myoclonic jerks, spasticity, dystonia, ataxia, visual disturbances, and incontinence in a sexagenarian woman with SSPE manifested 58 years after she had measles in childhood.

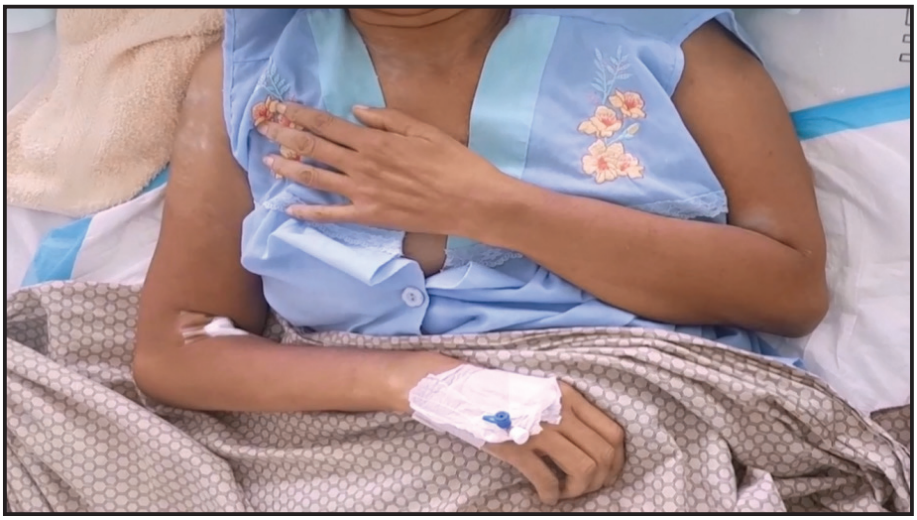
Case Report

A 62-year-old previously well secretary developed rapidly progressive dementia, myoclonic jerks, spasticity, dystonia, ataxia, visual disturbances, and fecal and urinary incontinence over a period of 6 months. She was initially diagnosed as having a major depressive disorder for which she was admitted to the psychiatric ward for 1 month. Due to nonresponsiveness to antipsychotic medications and a worsening neurological status, she was referred to a neurologist for further evaluation. There was no history of previous psychiatric illness, headache, stroke, seizures, or other neurological disease. She had no history of previous surgery, exposure to chemicals, use of recreational drugs, consumption of alcohol, or recent travel abroad. She was monogamic, heterosexual, previously married for 30 years, nulliparous, and now divorced. Family history was unremarkable. There was a history of measles at the age of 3 years. Folstein's Mini-Mental State Examination (MMSE) score was 0/30 with compromised orientation to time and place, registration, recall, attention, calculation, language, repetition, and

complex commands but preservation of orientation to person. The patient was afebrile, normotensive, and had a normal heart rate. The rest of the examination showed generalized intermittent hypertonia with hyperreflexia, symmetrical and bilateral cogwheel rigidity at the wrists, upper limb myoclonus, spasticity in all four limbs, and hypersomnolence. Gag reflex was diminished. Power was 5/5 in all limbs according to the Medical Research Council Scale for muscle strength. There was apathy with no frontal release or cerebellar signs. Proprioception, vibration, and sensory testing were intact. The involuntary motor activity phenomenology consisting of myoclonus (Video 1), predominantly observed in the upper limbs, was responsive to the combination of clonazepam and valproic acid. Dystonia and spasticity were also present. She remains without relapse of these manifestations 3 months later (Video 1 after treatment). Fundoscopy did not show any evidence of pigmentary retinal



Video **1.** **Phenomenology: Segment 1. The patient with SSPE at admission:** The involuntary motor activity consisted of abnormal, sudden, segmental, brief multifocal, and predominantly distal muscle jerks involving the patient's upper limbs more on the left than the right side. The phenomenon was observed purely in wakefulness. It was accompanied by dystonia of both legs with the knees flexed at 90°. The patient tried to stop the abnormal movement disorder unsuccessfully using the right hand which was only partially involved. The myoclonic jerks usually commenced sharply in the first hour of awake and remained unchanged throughout wakefulness. There was an observable pattern of one to two sequences of muscle contractions every 2–3 seconds continuously. This phenomenon occurred numerous times every day for 15 days.



Video **1.** **Segment 2. The patient from Segment 1 at Follow-up:** These myoclonic jerks, dystonia, and spasticity responded completely to the treatment with a combination of clonazepam 0.5 mg and valproic acid 200 mg orally twice daily. At 3 months of follow-up and with compliance to treatment, these movements have not returned.

changes, papilledema, or optic atrophy. Examination of other organ systems was unremarkable. Extensive investigations ruled out metabolic, autoimmune, vasculitis, neoplastic, and other infectious diseases (Table 1 submitted as supplemental file 1). Serum measles IgG was very high at 4237.31 IU/L (reference range ≥275 IU/L positive). A computerized tomography scanning (CT scan) of the brain, chest, abdomen, and pelvis was normal. Cranial magnetic resonance imaging (MRI) showed diffuse brain atrophy (Figure 1A) and mild subcortical enhancement in the right parietal lobe (Figure 1B). There was also asymmetric multiple hyperintensities best noted in the right temporoparietal region (Figure 1C), mesial temporal lobes (Figure 1D), and frontal lobes bilaterally (Figure 1E). An electroencephalogram (EEG) showed a poorly sustained background with frequent intermittent slow delta wave activity with a frequency of approximately 4 per second observed in the frontal areas bilaterally (Figure 2 submitted as Supplemental file 2). There was no seizure activity or a burst suppression pattern. Serum HIV rapid test, Mantoux test, and QuantiFERON test were negative. Vasculitis and autoimmune blood test screens were also negative. The cerebrospinal fluid (CSF) was clear and colorless with an opening pressure of 13.5 cm of water (reference range 6–25 cm of water) and glucose level of 54.0 mg/dL (reference range 50.0–80.0 mg/dL). The CSF protein level was elevated at 58 mg/dL (reference range 5–40 mg/dL), and the cell count was nil. CSF Gram stain, india ink acid fast, culture, and cytology were negative. Venereal Research Laboratory Test, and Toxoplasma gondii IgG and IgM antibodies in

Table **1.** **Medical Investigations**

Blood Test	**Result**	**Reference Range**
White cell count (WBC), eosinophils, hemoglobin, mean corpuscular volume, platelets count, and fasting blood sugar	Normal range	Normal or abnormal
Serum creatinine, BUN, uric acid, sodium, potassium, alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyltranspeptidase	Normal range	Normal or abnormal
Alkaline phosphatase, albumin, albumin-corrected calcium, thyroid function tests (TSH, free T3, total T3, free T4), serum vitamin B12 and folate levels	Normal range	Normal or abnormal
Lactate dehydrogenase	430 IU/L	105–333 IU/L
C-reactive protein (CRP)	31.1 mg/dL	0.0–1.0 mg/dL
Antistreptolysin O Titer	90 IU/mL	0–200 IU/mL
Venereal disease research laboratory (VDRL) test, fluorescent treponema pallidum antibody absorption (FTA-ABS), and ELISA for HIV test	Non-reactive	Nonreactive or reactive
Antibodies: Antithyroid peroxidase, herpes virus 1 and 2 IgG and IgM, cytomegalovirus (CMV) IgG and IgM, Epstein–Barr virus (EBV) IgG and IgM, hepatitis BS AG, hepatitis C IgG and IgM, Toxoplasma gondii IgG and IgM, and Echinococcus granulosus IgG	Negative	Positive or negative
Anti-double-stranded DNA, antinuclear antibody, antinuclear factor, perinuclear antineutrophil cytoplasmic antibody, cytoplasmic antineutrophil cytoplasmic antibody, and anti-GAD antibody	Negative	Positive or negative
Serum measles IGG	4237.31 IU/L	Positive: ≥275 IU/L
Serum measles IGM	0.09 IU/L	Negative: Less than 0.8 IU/L
Urine test	**Result**	**Reference range**
Physical, macroscopic, and microscopic urine analysis	Normal	Normal or abnormal
Urine culture	Negative	Positive or negative
An 8-point toxicology screen	Negative for cocaine metabolite, opiates, amphetamine, tetrahydrocannabinol, ethanol, phencyclidine, benzodiazepines, and barbiturates	Positive or negative

Table 1 continued

Table **1.** (*Continued*) **Medical Investigations**

Cerebrospinal fluid (CSF) investigations: Lumbar puncture performed on day 8th from admission	**Result**	**Reference range**
Appearance, opening pressure, and glucose	Normal	Normal or abnormal
Protein	58 mg/dL	5–40 mg/dL
Cell count: White blood cells, lymphocytes, polymorphous/ pus cells, red blood cells, epithelial cells, yeast cells	Nil	Normal: 0–5 cells/mm^3
Gram stain, india ink acid fast, culture, cytology	Negative	Normal: Negative
Toxoplasma gondii IgG and IgM antibodies	Negative	Positive or negative
Measles IGG in CSF	4017.91 IU/L	Positive: ≥275 IU/L
Measles IGM in CSF	0.09 IU/L	Negative: Less than 0.8 IU/L
VDRL and FTA-ABS	Nonreactive	Nonreactive or reactive
India ink test for *Cryptococcus neoformans* and HTLV 1 and 2, and anti-GAD antibody	Negative	Negative or positive
Oligoclonal bands in CSF	Positive 6 oligoclonal bands detected in CSF but none was detected in serum.	Negative or positive
Real-time PCR test for *Escherichia coli*, *Hemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitides*, *Streptococcus agalactia*, *Streptococcus pneumonia*, Cytomegalovirus DNA, *Enterovirus*, Herpes simplex virus 1, Herpes simplex virus 2, Human herpes virus 6, human parechovirus, Varicella zoster virus, *Cryptococcus neoformans* gattii.	Not detected	Detected or not detected
Other investigations	**Result**	**Reference range**
Mantoux test and QuantiFERON test for tuberculosis	Negative	Positive or negative
Electrocardiogram, chest X-ray, and echocardiogram	Normal	Normal or abnormal
Abdominal and pelvic ultrasound, and KUB ultrasound	Uterine fibroid otherwise normal	Normal or abnormal
CT scan of the brain, chest, abdomen, and pelvis with contrast and MRA/MRV scan of the brain	Normal	Normal or abnormal
Magnetic resonance imaging (MRI) scan of the brain	Abnormal	Normal or abnormal
Scalp electroencephalogram (EEG)	Abnormal	Normal or abnormal
Electromyography (EMG) and nerve conduction studies, video-EEG, polysomnography, and jerk-locked back averaging studies	Tests not obtained	Normal or abnormal

Abbreviations: BUN, Blood Urea Nitrogen; CSF, Cerebrospinal Fluid; CT, Computed Tomography; DNA, Deoxyribonucleic Acid; ELISA, Enzyme-Linked Immune Sorbent Assay; Free T3, Free Triiodothyronine; Free Total T3, Free Total Triiodothyronine; Free T4, Free Thyroxine; HPF, Microscopic High Power Field; MRA, Magnetic Resonance Angiography; PCR, Protein Chain Reaction; TSH, Thyroid-Stimulating Hormone.

serum and CSF were also negative. CSF measles IgG was very high at 4017.91 IU/L (reference range ≥275 IU/L positive). CSF real-time protein chain reaction (PCR) test for several bacterial and viral infections were negative. Serum and CSF anti-GAD antibodies were negative. Our patient was diagnosed with SSPE because three out of the five diagnostic criteria as proposed by Dyken were present.[4] These were characteristic clinical presentation with progressive dementia and myoclonic jerks, the presence of elevated levels of measles IgG antibodies in the serum and CSF, and the positive detection of six IgG oligoclonal bands in the CSF without finding any in serum.[4] After 3 months, the disease responded partially to treatment with interferon and isoprinosine. Currently, the patient is free from myoclonus, dystonia, spasticity, and visual disturbances. The MMSE score improved to 12/30 with a major impact on orientation to person, time and place, attention, language, and repetition. She continues to be disabled due to her inability to ambulate, perform independent activities of daily living and socialize. She is still having urinary and fecal incontinence. The patient was transferred to an outpatient neurology clinic for rehabilitation and follow-up care.

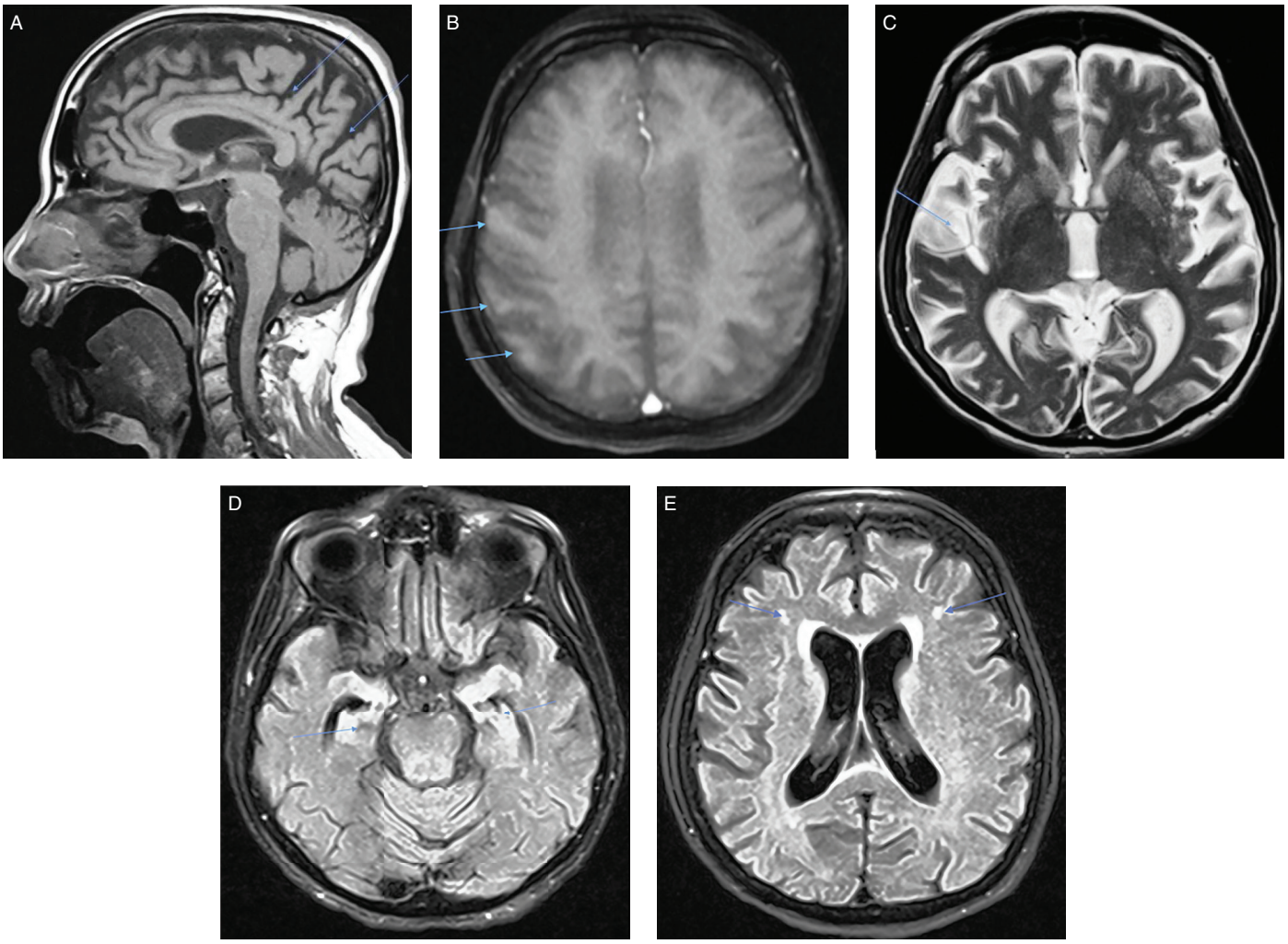


Figure 1. **Photographs of the MRI scan of the brain of the patient with SSPE.** (A) Sagittal magnetic resonance imaging (MRI) T1-weighted image of the brain showing diffuse atrophy. (B) Axial T1-weighted post-IV gadolinium showing mild subcortical enhancement in the right parietal lobe (blue arrows). (C) Axial MRI T2-weighted image of the brain showing asymmetric hyperintensities best noted in the right temporoparietal region (blue arrows). (D) Axial MRI T2-FLAIR-weighted image of the brain showing diffuse hyperintensities in mesial temporal lobes bilaterally (blue arrows). (E) Axial MRI T2-FLAIR-weighted image with hyperintensities best seen in the frontal lobes (blue arrows) bilaterally.

Discussion

SSPE presents predominantly in the childhood and early adolescent groups, with rare cases of onset at 25, 49, 52, and 61 years old.[5–7] SSPE with an onset in a sexagenarian is rare, but it has been considered underdiagnosed and underreported as a cause of dementia. The differential diagnosis of subacute dementia and/or myoclonus in adults can be summarized into genetic, neoplastic, paraneoplastic, inflammatory-autoimmune, neurodegenerative, neuroinfection, CNS trauma, CNS vasculopathies, toxicity, organ failure, nutritional endocrine, and acquired metabolic-related causes. Some specific clinical differential diagnosis of SSPE includes variant Creutzfeldt-Jakob Disease (CJD), autoimmune encephalitis, neuroinfectious diseases, Hashimoto's encephalopathy, paraneoplastic syndromes, leukodystrophies, and atypical forms of multiple sclerosis (MS). The history, MRI, serum, and CSF findings were not in keeping with CJD, stroke, CNS vascular diseases, CNS trauma, space occupying lessons, Alzheimer's disease, dementia with Lewy Body disease, progressive supranuclear palsy, corticobasal degeneration, acquired immunodeficiency syndrome, and nutritional deficiencies. A negative real-time PCR test for neuroinfectious diseases ruled out most of them. The patient did not meet Mc Donald Criteria for MS. The absence of a history to chemical exposure and a negative six points toxicology test ruled out toxicity. Blood investigations ruled out vasculitis, autoimmune, and most endocrine diseases. Hepatorenal end-organ failure was also ruled out. However, the presence of antibodies against measles, in both serum and CSF, made other analyses unnecessary. Clinical manifestations and evolution, medical history and investigations, response to treatment, and specific patient fulfillment of three out of five Dyken's criteria for the diagnosis of SSPE established

the diagnosis.[4] Ophthalmological abnormalities with SSPE include papilledema, papillitis, optic atrophy, macular or perimacular chorioretinitis, macular pigment disturbances, cortical blindness, and Anton's syndrome.[8] However, despite the presence of visual disturbances, such as changes in visual acuity and diplopia, fundoscopy in our patient was normal. Visual disturbances resolved gradually after the initiation of treatment.

There are no specific brain MRI findings for SSPE and MRI features depend mostly on the evolution of the disease. Asymmetrical white matter involvement, more prominently in the posterior regions of the brain, may be seen in the early course of the disease and contrast enhancement in the affected regions is not unusual. As the disease progresses, more extensive white matter and cortical involvement ensue with additional corpus callosum and basal ganglia involvement resulting in a global encephalomalacia.[9–11] Some of these findings were noted in our patient. These findings may suggest ischemic changes after demyelination.[10,11] Mesial temporal lobes hyperintensities were also noted (Figure 1D). Although mesial temporal lobes involvement is atypical in SSPE and can lead to uncertainty surrounding diagnosis, this MRI pattern has been previously documented in patients with classic clinical manifestations of the disease.[12] The clinical significance of this specific MRI finding is currently unknown.[12] Periventricular and subcortical hyperintensities in SSPE have also been reported extensively. This progression from cortical structures extending down to the midbrain was described by Alkan et al. in a case–control study of 18 patients and 11 age-matched controls who underwent MRI and diffusion-weighted imaging.[13] The direct correlation between MRI findings and clinical progression in SSPE remains an enigma in the literature.[13] Although extrapyramidal features are common in the advanced course of the disease in the form of generalized rigidity, choreoathetoid movements, and hemiballismus, only a few patients have manifested dystonia. To date, uncommon presenting features have been described such as tremor, dystonia, and hemiparkinsonism.[14] Misra et al. reported early onset parkinsonian features in two patients.[15] Migratory basal ganglia lesions in SSPE have been reported and axonal spread of the virus from the substantia nigra has been implicated in producing parkinsonian symptoms.[16] Some of these signs of parkinsonism such as symmetrical and bilateral cogwheel rigidity at the wrists and spasticity in all four limbs were also noted in our patient. Burst suppression is the typical characteristic EEG pattern observed in 65% to 83% of individuals with SSPE. Burst suppression are periodic EEG complexes characterized by periods of high-voltage electrical activity alternating with periods of minimal or no activity in the brain such as seen in patients under general anesthesia, coma, or hypothermia. Characteristically, the periodic complexes consist of bilaterally symmetrical, synchronous, high voltage (200–500 mV) bursts of polyphasic, and stereotyped delta waves. Waveforms remain identical in any given lead. These periodic complexes repeat at fairly regular 4–10 seconds intervals and may have a 1:1 relationship with myoclonic jerks. On the contrary, scalp EEGs have been reported normal among patients suffering from SSPE, especially at the early course of the disease. The abnormal EEG observed in our patient (Figure 2 submitted as Supplemental file 2) showed a poorly sustained background with frequent intermittent slow delta wave activity with a frequency of approximately 4 per second observed in the frontal areas bilaterally. These EEG findings are not typical of SSPE. This EEG pattern may be seen in patients with a metabolic or infective encephalopathy, a degenerative process, or a disturbance of the thalamo cortical nerve fibers, but it can also be seen late in the course of SSPE. Brain biopsies or postmortem histopathological examination in cases of SSPE revealed evidence of astrogliosis, neuronal loss, degeneration of dendrites, demyelination, neurofibrillary tangles, and infiltration of inflammatory cells.[17–19] Although myoclonic jerks, spasticity and dystonia responded rapidly and completely to the combination of clonazepam and valproic acid in our patient, these manifestations have been reported to respond appropriately to other medications such as carbamazepine and levetiracetam.[16–22]

The measles virus can remain dormant in the CNS for years, on average 4–10 years following acute measles infection in childhood and early adolescence. However, the latency period is longer in adults in whom the mean age at presentation is 20 years 11 months.[17] In our case, the virus remained dormant for 58 years after the acute measles infection. Measles infection can produce extensive perivascular infiltrates throughout the brain. The terminal manifestation of the infection can produce nerve cell degeneration, neuronal loss, astrogliosis, degeneration of dendrites, demyelination, neurofibrillary tangles, and infiltration of inflammatory cells throughout the frontal, parietal, temporal and occipital cortex, basal ganglia, thalamus, pons, and medulla.[22,23] According to the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety, the incidence of SSPE is approximately 4–11 cases per 100,000 cases of measles, although with measles infection acquired very early in life the risk may be higher (18 per 100,000 cases).[24] According to the World Bank, the rate of measles vaccination among children aged 12–23 months in Trinidad and Tobago was reported at 86% in 2016 and at 93% in 2017 for a population of 1,328,019. However, Trinidad and Tobago remains at risk for the reintroduction of measles due to regular travel.[25]

Prognosis in our patient is uncertain. According to the literature, only 5% of individuals with SSPE undergo spontaneous remission, with the remaining 95% dying within 5 years of diagnosis.[19–22]

In conclusion, SSPE can initially present with predominant psychiatric features and personality change and this case serves as a reminder that it should be included in the differential diagnosis of older patients presenting with rapidly progressive dementia. Treatment remains a challenge. The vaccination drive for the global eradication of measles is imperative and the only effective strategy to prevent SSPE.

Authors' contributions

The authors contributed equally to this work.

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