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Tremor and Other Hyperkinetic Movements

In Response to:

Reyes AJ, Ramcharan K, Perot S, Giddings SL, Rampersad F, Gobin R. Subacute Sclerosing Panencephalitis Causing Rapidly Progressive Dementia and Myoclonic Jerks in a Sexagenarian Woman. Tremor Other Hyperkinet Mov. 2019; 9. doi: 10.7916/tohm.v0.680

Editorials

Subacute Sclerosing Panencephalitis in Older Adulthood

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Subacute sclerosing panencephalitis (SSPE) is a devastating brain disorder that typically affects children and adolescents. SSPE is caused by persistent measles virus infection. The mechanisms that facilitate the measles virus entering the brain, and persisting and proliferating there for very long periods are not precisely known. Once inside the brain, the measles viral genome undergoes a series of mutations, particularly in the M and F protein genes. These mutations are considered responsible for viral persistence and transneuronal spread inside the brain. Measles viral genome isolated from human brain tissues demonstrates clustered mutations in the virus genome, particularly in the M gene. These mutations destroy the structure and functioning of the encoded proteins. Complete infectious virus particle has rarely been demonstrated in the brain tissue.[1] In the brain, the mutated measles virus triggers an intense inflammatory reaction that leads neuron destruction.

SSPE usually affects children. The incidence of SSPE in any population is roughly proportional to that of measles. Developed countries have observed a considerable decline in the occurrence of new SSPE cases following implementation of universal vaccination programs against measles. A World Health Organization expert committee reviewed the epidemiology of SSPE and observed that approximately 4–11 cases of SSPE occur per 100,000 cases of measles.[2] The risk of SSPE is much higher with measles infection occurring very early in life (less than 2 years of age).[2] Many South East Asian countries, like India and Pakistan, seem to have a very high incidence of SSPE. In developed, resource-rich nations, re-emergence of SSPE is recorded after outbreaks of measles, following a period of excellent measles control.[1]

Clinically, SSPE is characterized by diffuse encephalitis. Characteristic clinical manifestations area declines in cognitive function, periodic myoclonus, gait abnormalities, vision loss, and lastly a vegetative state. Ocular complications such as chorioretinitis, optic atrophy, papillitis, papilledema, visual field defects, and cortical blindness are frequently heralding manifestations of SSPE.[1]

Electroencephalography (EEG) shows periodic stereotyped discharges and is virtually pathognomonic of SSPE. Neuroimaging is often nonspecific; however, periventricular white matter signal changes are a characteristic magnetic resonance imaging (MRI) abnormality. In the late stages of disease, there is marked cerebral atrophy. A definite diagnosis of SSPE is made if elevated measles antibodies are demonstrated in cerebrospinal fluid. Currently, there is no effective treatment available for SSPE.[1]

SSPE in adults is unusual and often presents with atypical features. In a series of 39 adult-onset cases of SSPE, in addition to myoclonus,

Table 1. A review of adult-onset subacute sclerosing panencephalitis

Reference	Country	Age/ sex	Duration of illness	Clinical presentation	Myoclonus	EEG	Neuroimaging	Treatment	Outcome	Basis of diagnosis
Reyes et al 2019[4]	Trinidad and Tobago, (West Indies)	62/F	six months	Rapidly progressive dementias	Present	Intermittent slow delta wave activity	Asymmetric multiple T2 hyperintensities	Interferon and isoprinosine	Mild improvement	Elevated CSF antimeasles antibody titre
Gokoglu and Gozdas 2019[5]	Turkey	62/F	3 years	Behavioural changes and deterioration of mental status	Absent	Diffuse background slowing	Subcortical and periventricular deep white matter signal changes	Amantadine 300/day	Some improvement	Elevated CSF antimeasles antibody titre
Elmali et al. 2018[6]	Turkey	61/F	2 years	Behavioural, cognitive changes and seizures	Subtle	Periodic generalized complexes	Old cerebral, thalamic and brainstem infarcts	Symptomatic	Not available	Elevated CSF antimeasles antibody titre
Tanaka et al. 1987[7]	Japan	52/M	4 years	Rapidly progressive mental deterioration	Present	Periodic discharges	Not available	Not available	Died	Elevated CSF antimeasles antibody titre. Brain-biopsy: neuronal loss, glial proliferation, and perivascular lymphocytic cuffing. Numerous intranuclear inclusions nucleocapsids of paramyxovirus
Studart Neto et al. 2015[8]	Brazil	50/M	8 years	Behavioural changes and deterioration of mental status	Absent	Diffuse background slowing	Hyperintense lesions involving subcortical, deep hemispheric, and pontine white matter	Not available	After 15 months, the patient was in a vegetative state	Brain biopsy staining for measles was positive in neuronal, astrocyte, oligodendrocyte and lymphocyte
Gagnon and Bouchard 2003[9]	Canada	49/M	2 years	Behavioural changes and progressive cognitive impairment	Present	Periodic sharp and slow-wave discharges	Hyperintensities in both periventricular and subcortical white matter	High-dose intrathecal interferon alfa and oral isoprinosine for 6 weeks	Continuous deterioration	Elevated CSF antimeasles antibody titre

Table 1 continued

Table 1. (*Continued*) **A review of adult-onset subacute sclerosing panencephalitis**

Reference	Country	Age/ sex	Duration of illness	Clinical presentation	Myoclonus	EEG	Neuroimaging	Treatment	Outcome	Basis of diagnosis
Croxson et al. 2002[10]	Australia	43/M	3 years	Vision loss and cognitive decline		Irregular delta activity	White-matter changes and focal tissue loss in the medial occipital lobes and inferior left parietal lobe	Corticosteroids	Died	Elevated CSF antimeasles antibody titre. Brain biopsy Measles virus RNA found in brain, spinal cord and eye
Dubois et al 2005[11]	Belgium	42/F	4 years	Severe cognitive deficit, ataxia and spasticity	Absent	Diffuse slowing	Multiple confluent periventricular hyperintensities	Not available	Not available	Elevated CSF antimeasles antibody titre
Baillif et al. 2012[12]	France	39 M	3 years	Chorioretinitis 3 years before behavioural changes and deterioration of mental status	Absent	Nonspecific generalized slowing	Parieto-occipital signal changes	Isoprinosine, Interferon Alpha, and ribavirin	Rapid progression to death in 3 months	Elevated CSF antimeasles antibody titre
Frings et al. 2002[13]	Germany	39/F	3 years	Progressive cognitive impairment	Absent	Normal	Progressive generalized cerebral atrophy	Not available	Not available	Elevated CSF antimeasles antibody titre
Jeevagan and Dissanayake 2017[14]	Sri Lanka	36/M	2 years	Chorioretinitis 2 years before behavioural changes and deterioration of mental status	Absent	Generalised intermittent slowing	T2 hyperintensities in periventricular region predominantly affecting the occipitoparietal lobes	Short course of oral corticosteroids	No improvement	Elevated CSF antimeasles antibody titre

Based upon a PubMed search and review of all cases of subacute sclerosing panencephalitis where the age of onset was greater than 35years.

behavioral changes, seizures, and cognitive issues, visual and extrapyramidal disturbance were common presenting manifestations. In this study, mean age at diagnosis was approximately 21 years (range 18–43 years).[3] We reviewed all published cases of SSPE where the age of onset was greater than 35 years. Behavioral changes and deterioration of mental status were the commonest presentations. Vision loss was the next most commonly encountered symptom. Periodic myoclonus and periodic EEG discharges were not consistently present. MRI consistently demonstrated T2 hyperintensities in the periventricular region, predominantly affecting the occipitoparietal lobes (Table 1).[4–14] Creutzfeldt–Jakob disease and anti-*N*-methyl-D-aspartate-receptor encephalitis are often close differential diagnoses. The demonstration of elevated CSF antimeasles antibody titer and brain biopsy helps in establishing the diagnosis of SSPE. In six patients, histopathological findings of autopsied/biopsied brain were available. In three cases, components of measles virus genome, in brain tissue, were demonstrated (Table 1).[7,8,10]

Reyes and colleagues reported a 62-year-old woman who presented with rapidly progressive dementia and myoclonus and was later diagnosed as having SSPE.[4] This is one of the three oldest recorded patients with SSPE. There are two additional earlier reports of SSPE where patients presented after the age of 60 years.[5,6] All these three cases presented with progressive cognitive decline.

Measles is still common in many developing countries, particularly in Africa and Asia. In 2017, the world has seen approximately 110,000 measles-related deaths. Even in developed, resource-rich countries, periodic outbreaks of measles take place. In 2019, the World Health Organization received a report of 112,163 measles cases from 170 countries.[15] Measles was declared eliminated from the United States in 2000, although there have been recent outbreaks. It is likely that many new cases of adult-onset SSPE, particularly in older adults, will continue to be reported from all parts of world, including developed countries.

Many antiviral and immune modulator drugs like isoprinosine, interferon-alpha, and ribavirin are used to stabilize the course of disease. Patients with SSPE die within 1–3 years of diagnosis. In acute fulminant SSPE, patients die much earlier. Many genetic mutations in the measles fusion (F) protein change it to a biologically active fusogenic form of the F protein. The fusogenic form of the F protein facilitates transneuronal spread of measles virus across neurons. A fusion inhibitor peptide would be a valuable potential therapeutic option to treat SSPE.[1]

In conclusion, SSPE in older adults remains a diagnostic possibility both in resource-rich developed counties and in countries where measles is still endemic. SSPE in older patients is likely to present with atypical clinical features, and characteristic myoclonus and periodic EEG changes may not be present. A high index of suspicion and appropriate workup is essential for early diagnosis. There is a need to include cerebrospinal fluid antimeasles antibody titer estimation in the workup of progressive dementia, particularly in patients with myoclonus or periodic EEG abnormalities.

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