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Subacute Sclerosing Panencephalitis (SSPE)

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Abstract

Subacute sclerosing panencephalitis (SSPE) is a rare, progressive neurodegenerative disorder that arises as a late complication of measles virus infection, typically 7-10 years post-exposure. Despite the availability of effective measles vaccines, SSPE remains a significant concern, particularly in regions with fluctuating vaccination rates. This review explores the pathophysiology, clinical presentation, diagnostic criteria, and treatment options for SSPE, emphasizing the disease's progression and current management strategies.

The pathophysiology of SSPE involves the persistent presence of the wild-type measles virus in the central nervous system, leading to a cascade of neuronal destruction and neurological deterioration. Clinically, SSPE manifests through a four-stage progression: initial cognitive decline and behavioral changes, followed by movement disorders and seizures, and culminating in severe neurological deficits and vegetative states. Diagnosis is primarily based on patient history, clinical symptoms, and laboratory findings including elevated anti-measles antibodies in cerebrospinal fluid, characteristic electroencephalographic patterns, and MRI abnormalities.

Current treatment modalities are primarily symptomatic, including the use of antiviral agents such as isoprinosine and ribavirin, with varying degrees of success. Research into novel therapies and optimal treatment regimens continues, focusing on improving patient outcomes and extending survival. Additionally, there is an urgent need for increased vaccination coverage and public health initiatives to prevent measles and, consequently, SSPE.

In conclusion, while SSPE remains a devastating condition with limited treatment options, proactive vaccination strategies and ongoing research are crucial for the prevention and management of this severe sequela of measles infection.

Keywords: Subacute Sclerosing Panencephalitis; Measles; Neurodegeneration; Diagnosis; Treatment; Vaccination

Abbreviations

SSPE: Subacute sclerosing panencephalitis; CSF: Cerebro Spinal Fluid; IgG: Immunoglobulin G; EEG: electroencephalogram.7

Introduction

Measles is an airborne disease caused by an RNA virus of the Paramyxoviridae family [1]. Subacute sclerosing panencephalitis (SSPE) is a progressive neurodegenerative

disorder resulting from the persistence of the measles virus, typically occurring 7-10 years after the initial infection [2]. SSPE predominantly affects children and young adults.

Measles is a highly contagious viral infection characterized by acute fever caused by the measles virus [3]. It can lead to various complications, including rare conditions like subacute sclerosing panencephalitis (SSPE), which typically manifests years after the initial infection. SSPE was first noted in medical literature in the early 20th century but its association with the measles virus was definitively established in 1965 through electron microscopy studies by Bouteille, et al. [4].

Despite effective vaccination reducing the incidence of SSPE, cases still occur, particularly in developing regions and occasionally in developed countries where vaccination rates fluctuate [5]. SSPE primarily affects young males around the age of 12, presenting with a range of symptoms such as psychiatric abnormalities, cognitive decline, seizures, myoclonus, visual impairments, and movement disorders [6].

Diagnosis involves specific EEG patterns known as Radermecker complexes, abnormal CSF findings including elevated IgG antibodies specific to measles, and sometimes imaging showing changes in brain structures like the basal ganglia or white matter [6-8]. Treatment focuses on managing symptoms such as seizures and movement disorders, with therapies like interferon-alpha and inosiplex showing variable effectiveness [9].

SSPE progresses relentlessly, often leading to severe outcomes like akinetic mutism and coma in advanced stages. Clinical staging categorizes SSPE into four stages based on symptom progression, from cognitive issues in early stages to profound neurological deficits in later stages [10]. Movement disorders, although previously underestimated, are increasingly recognized as significant features of the disease, impacting overall clinical outcomes. This review synthesizes current knowledge on movement disorders in SSPE, their evolution, and their implications for disease management [11].

Pathophysiology

Measles is transmitted through nasopharyngeal secretions [12]. Acute complications of measles include diarrhea, otitis media, pneumonia, and postinfectious encephalitis [13]. Neurological complications can involve post-measles encephalitis, measles inclusion body encephalitis, transverse myelitis, and SSPE [14]. In SSPE, the measles virus invades the cerebrum, leading to neuronal destruction. The exact mechanism of SSPE development is not fully understood. Genetic studies indicate that wild strains of the measles virus, not the vaccine strains, are responsible for SSPE [15]. The younger the patient at the time of measles infection, the higher the risk of developing SSPE.

Clinical Presentation

The clinical course of SSPE includes progressive cognitive decline and behavioral changes, followed by focal or generalized seizures [16]. The clinical progression of subacute sclerosing panencephalitis (SSPE) is characterized by gradual cognitive decline and behavioral changes, often followed by focal or generalized seizures, myoclonus, ataxia, visual disturbances, and eventual vegetative state [17,18]. While rare cases of spontaneous long-term remission have been reported, most patients succumb to the disease within a few years of onset [17,19].

Jabbour et al. categorized the clinical manifestations of SSPE into four stages: Stage I includes irritability, dementia, social withdrawal, lethargy, and speech regression; Stage II involves movement disorders such as dyskinesia, dystonia, and myoclonus; Stage III presents with extrapyramidal symptoms, decerebrate posturing, and spasticity; Stage IV is marked by cortical dysfunction leading to vegetative state, autonomic failure, and akinetic mutism [20].

Atypical presentations of SSPE have also been documented, including isolated psychiatric manifestations, poorly controlled seizures, and isolated extrapyramidal symptoms like dystonia and chorea [21,22]. Occasionally, SSPE may present with a stroke-like onset, and some patients experience transient plateau periods or slight improvement, although the disease typically follows a relentless course with high mortality [21]. The differential diagnosis of SSPE includes early-stage epilepsy, psychiatric disorders, other viral encephalitides, atypical multiple sclerosis, leukodystrophies, variant Creutzfeldt-Jakob disease, and neurometabolic encephalopathies [23,24].

Visual impairment, including focal necrotizing macular retinitis, is a common ocular manifestation in SSPE, occurring in nearly 50% of cases [25]. Ophthalmic symptoms may precede neurological symptoms, and other ocular findings can include retinal hemorrhages, edema, detachment, and optic disc changes such as papillitis and pallor [25].

Diagnosis

Diagnosis of SSPE is based on patient history and clinical presentation, supplemented by imaging and laboratory studies. MRI of the brain reveals decreased gray matter volume, especially in the frontotemporal cortex, amygdala, and cingulate gyrus [26]. SSPE relies on Dyken's criteria,

comprising two major and four minor criteria. Major criteria include: 1) elevated anti-measles antibody levels in cerebrospinal fluid (CSF) (≥1:4) or serum (≥1:256), and 2) typical or atypical clinical presentations. Typical presentations encompass acute, rapidly progressive, subacute progressive, chronic progressive, or chronic relapsing-remitting courses, while atypical presentations involve seizures, prolonged Stage I, or an unusual age of onset (infancy or adulthood) [27,28]. Minor criteria consist of: 1) characteristic electroencephalographic findings such as periodic slow-wave complexes (Radermecker complexes), 2) CSF globulin levels exceeding 20% of total CSF protein, 3) distinct histopathological findings on brain biopsy indicating necrotizing leukoencephalitis with inflammatory changes, viral inclusion bodies, neuronal loss, and astrocytosis, and 4) specialized molecular diagnostic tests identifying mutated wild-type measles virus genome. Diagnosis typically requires fulfillment of two major criteria and one minor criterion; however, atypical cases may necessitate histopathological or molecular evidence [27,29,30]. Interestingly, post-mortem histopathological studies have revealed approximately 20% of individuals without SSPE showing detectable measles virus in the brain. Nevertheless, the presence of viral RNA alone without meeting Dyken's criteria does not confirm SSPE [31].

Neuroimaging, while not pathognomonic for SSPE, can provide supportive evidence. Early-stage magnetic resonance imaging (MRI) may demonstrate reduced gray matter volume in specific brain regions such as the frontotemporal cortex, amygdala, and cingulate gyrus [32]. Disease progression may manifest as hyperintensities on T2-weighted images in the cerebral cortex, periventricular white matter, basal ganglia, and brainstem, eventually leading to diffuse cortical atrophy characterized by enlarged sulci and ventriculomegaly. MR spectroscopy findings may include initial increases in choline-to-creatine and inositol-to-creatine ratios, along with normal N-acetyl aspartate-to-creatine ratios, progressing to decreased N-acetyl aspartate-to-choline and N-acetyl aspartate-to-creatine ratios correlating with brain volume loss [33,34].

Treatment

Subacute sclerosing panencephalitis (SSPE) represents a severe, often fatal disease without a known cure, despite advancements in antiviral and immunomodulatory medications. Typically, patients face a mortality risk within four years of onset, although targeted therapies offer hope for extended survival. In a survey across seven countries involving 500 SSPE patients, physicians commonly use isoprinosine alone or in combination with ribavirin as standard treatments. Other therapies like intravenous immunoglobulin, intrathecal alpha-interferon (a-IFN), and amantadine are also employed [35-41]. Research indicates promising outcomes with isoprinosine, with studies showing improved survival rates exceeding two years among treated patients [41,42]. Clinical trials comparing isoprinosine to intraventricular alpha-IFN have demonstrated positive responses in a significant proportion of cases, contrasting with low spontaneous remission rates reported elsewhere [4].

Treatment comparisons between isoprinosine alone and combined with intraventricular alpha-IFN reveal no significant differences in mortality [42,43]. Studies involving children have shown remission rates of up to 44% with certain combinations of medications, compared to negligible rates in control groups [42]. Beta-interferon (b-IFN) and ribavirin have shown modest clinical benefits, particularly when administered alongside isoprinosine [4]. However, definitive cure remains elusive, necessitating further research, including randomized controlled trials, to establish optimal treatment protocols [40,44].

Alternative interventions such as amantadine, cimetidine, intravenous immunoglobulin, plasmapheresis, and corticosteroids have shown varied effectiveness [35,38,39]. Newer therapies targeting viral fusion proteins are under development but require thorough evaluation before integration into standard SSPE management [35].

Symptomatic care involves multidisciplinary collaboration, including palliative care, parental support networks, and early intervention for feeding and sleep issues [36,37]. Specific medications like baclofen, sodium valproate, clonazepam, benzodiazepines, and leviteracetam are recommended for managing symptoms like spasticity and myoclonus [36,45].

Managing SSPE in HIV-coinfected children presents additional complexities, particularly concerning potential drug interactions and treatment guidelines tailored to specific regional contexts, such as sub-Saharan Africa [46].

Conclusion

SSPE, an avoidable disorder, underscores the crucial role of medical professionals as advocates for children, ensuring parents are well-informed and confident in the safety of vaccinations. Strong endorsement of vaccination programs by health professionals is vital to eradicating diseases like polio and measles, which no child should suffer from today. Health authorities must promptly address interruptions in childhood immunization to prevent future outbreaks. Given the recent global increase in measles cases, clinicians must maintain heightened awareness of SSPE's potential manifestations in affected children, facilitating early diagnosis through vigilance and specific investigations.

Treatment options, currently limited to immunomodulation and antiviral agents of marginal effectiveness, necessitate collaborative trials to evaluate new modalities. Resource limitations pose challenges, requiring multidisciplinary teams and costly medications. Further research into optimal antiepileptic drugs, particularly in immunocompromised children receiving antiretroviral therapy, is essential. Emulating policies that enhance vaccination coverage is critical until measles is globally eradicated, safeguarding children worldwide from SSPE.

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