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SUBACUTE SCLEROSING PANENCEPHALITIS IN CHILDREN

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Key words: subacute sclerosing panencephalitis, measles virus, neurological disorders, immunization, pediatric neurodegeneration.
Tayanch so‘zlar: o‘tkir osti sklerozlovchi panensefalit, qizamiq virusi, nevrologik kasalliklar, immunizatsiya, bolalardagi asab tizimi degeneratsiyasi.
Ключевые слова: подострый склерозирующий панэнцефалит, вирус кори, неврологические заболевания, иммунизация, детская нейродегенерация.

Subacute Sclerosing Panencephalitis (SSPE) is a progressive, fatal neurodegenerative disease caused by persistent infection with a mutated measles virus. This literature review examines the historical, clinical, epidemiological, and immunological aspects of SSPE, emphasizing the role of early diagnosis and vaccination. Despite advancements in antiviral and immunomodulatory therapies, effective treatment remains elusive, highlighting the need for ongoing research and public health measures. The review underscores the critical importance of sustained measles immunization programs to prevent the resurgence of SSPE in vulnerable populations.

BOLALARDA O‘TKIR OSTI SKLEROZLANUVCHI PANENSEFALIT

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O‘tkir osti sklerozlovchi panensefalit (O‘SSP) - mutatsiyaga uchragan qizamiq virusi bilan doimiy infeksiya tufayli kelib chiqadigan progressiv, o‘limga olib boruvchi neyrodegenerativ kasallik hisoblanadi. Ushbu adabiyotlar sharhida O‘SSPning tarixiy, klinik, epidemiologik va immunologik jihatlari o‘rganilgan bo‘lib, erta tashxis qo‘yish va emlashning ahamiyati alohida ta’kidlangan. Virusga qarshi va immunomodulyator terapiya sohasidagi yutuqlarga qaramay, samarali davolash usullari hanuzgacha topilmagan, bu esa uzluksiz tadqiqotlar va jamoat salomatligi choralarini o‘tkazish zarurligini ko‘rsatadi. Sharh aholining zaif qatlamlarida O‘SSPning qayta paydo bo‘lishining oldini olish uchun qizamiqqa qarshi barqaror emlash dasturlarining hal qiluvchi ahamiyatga ega ekanligini ta’kidlaydi.

ПОДОСТРЫЙ СКЛЕРОЗИРУЮЩИЙ ПАНЭНЦЕФАЛИТ У ДЕТЕЙ

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Подострый склерозирующий панэнцефалит (ПСПЭ) - это прогрессирующее, смертельное нейродегенеративное заболевание, вызванное персистирующей инфекцией мутировавшим вирусом кори. В данном обзоре литературы рассматриваются исторические, клинические, эпидемиологические и иммунологические аспекты ПСПЭ, подчеркивается роль ранней диагностики и вакцинации. Несмотря на достижения в области противовирусной и иммуномодулирующей терапии, эффективное лечение остается недостижимым, что указывает на необходимость продолжения исследований и принятия мер по охране общественного здоровья. Обзор подчеркивает критическую важность устойчивых программ иммунизации против кори для предотвращения возобновления ПСПЭ среди уязвимых групп населения.

Introduction. Understanding the significance of Subacute Sclerosing Panencephalitis (SSPE) in children, alongside a clearly defined research objective and systematic methodology for literature selection, is crucial for a comprehensive review of the disease. SSPE is a rare, progressive neurodegenerative disorder caused by a persistent measles virus infection, predominantly affecting children and young adults [1–3]. The disease is characterized by a complex interplay of viral persistence and host immune response, with genetic factors such as single-nucleotide polymorphisms influencing susceptibility and progression [1,4]. Despite the availability of effective measles vaccines, SSPE remains a concern due to vaccine hesitancy and disruptions in vaccination programs, which have led to increased incidence in certain regions [2,5]. The clinical presentation of SSPE includes cognitive decline, myoclonic seizures, and other neurological symptoms, with diagnosis often confirmed through elevated measles antibody titers in cerebrospinal fluid and characteristic EEG patterns [3,6,7]. The disease is particularly prevalent in areas with low vaccination coverage and among children who contracted measles at a young age [8]. A systematic approach to literature selection allows for a thorough understanding of SSPE's epidemiology, pathogenesis, and clinical management, highlighting the importance of vaccination as the primary preventive measure [5,7,8]. Furthermore, research into the immunogenetics of SSPE and the role of viral mutations provides insights into potential therapeutic targets, although current treatment options remain largely supportive [4,7]. By integrating these diverse aspects, a comprehensive review can

inform public health strategies and guide future research efforts to mitigate the impact of SSPE in children.

Historical overview. The discovery and initial clinical descriptions of Subacute Sclerosing Panencephalitis (SSPE) have significantly shaped our understanding of this rare, fatal complication of measles. SSPE is characterized by a progressive neurological decline, typically manifesting years after measles infection, with symptoms such as cognitive deterioration, myoclonic seizures, and eventual progression to a vegetative state [7,9]. The disease is caused by a persistent, defective measles virus, with a higher risk in children infected before the age of five [9,10]. Epidemiologically, SSPE incidence is closely tied to measles prevalence, with higher rates in regions with low vaccination coverage [7,11]. Historical data show that before widespread measles vaccination, SSPE was more common, but the introduction of the measles vaccine in the 1970s led to a dramatic decline in SSPE cases in high-income countries [12,13]. Despite initial concerns, extensive epidemiological and virological studies have confirmed that the measles vaccine does not cause SSPE, but rather, it prevents it by reducing measles infections [12]. In regions with poor vaccination coverage, such as parts of India and Papua New Guinea, SSPE remains a significant health issue, with incidence rates as high as 21 to 100 cases per million [9,10]. The pathophysiology of SSPE involves a defective immune response that allows the virus to persist in the brain, leading to chronic inflammation and neuronal damage [7,14]. Current management strategies focus on supportive care and seizure control, as there is no definitive cure, although some treatments like interferon and isoprinosine have shown limited benefits [14]. The global eradication of measles through vaccination remains the most effective strategy to eliminate SSPE, underscoring the critical role of vaccination programs in controlling this devastating disease [13,15].

Etiology and Pathophysiology. Subacute sclerosing panencephalitis (SSPE) is a rare, fatal neurodegenerative disease caused by the persistent infection of the central nervous system (CNS) by a mutant form of the measles virus (MeV). This condition typically manifests several years after an initial measles infection, particularly in children who contracted the virus before the age of two, as their immature immune systems are less capable of eradicating the virus completely[2,9]. The measles virus responsible for SSPE is characterized by specific mutations, particularly in the M, F, and H genes, which impair the virus's ability to produce infectious particles and facilitate its persistence in the brain [7,16]. These mutations confer hyperfusogenic properties to the virus, allowing it to spread transneuronally despite the absence of the typical receptors required for viral entry into neurons [7]. The immune response in SSPE is paradoxical; despite high levels of neutralizing antibodies in the serum and cerebrospinal fluid (CSF), the virus is not eradicated, suggesting a defect in cell-mediated immunity [10,17]. The presence of high measles IgG titers in the CSF, without detectable viral RNA, further supports the notion of an immune-mediated pathogenesis rather than active viral replication [17]. Clinically, SSPE progresses through stages, beginning with cognitive decline and myoclonus, advancing to severe neurological impairment and ultimately a vegetative state [18]. The inflammatory response in the brain, driven by the persistent viral presence, leads to extensive tissue damage and demyelination, as evidenced by neuroimaging and EEG findings [7]. Despite various therapeutic attempts, including antiviral and immunomodulatory treatments, the prognosis remains poor, with vaccination being the most effective preventive measure against SSPE [9,10].

Epidemiology. Subacute sclerosing panencephalitis (SSPE) is a rare, progressive neurological disorder caused by a persistent measles virus infection, predominantly affecting children and adolescents. The global prevalence of SSPE is closely linked to measles incidence, with higher rates observed in regions with low vaccination coverage, such as developing countries like India [3,8,19]. The incidence of SSPE has declined significantly in high-income countries due to widespread measles vaccination, but recent trends indicate a resurgence in some areas, possibly due to reduced vaccination rates exacerbated by the COVID-19 pandemic [5,7]. SSPE typically manifests in children aged 4 to 20 years, with a peak incidence between 7 and 10 years [20]. The risk is notably higher in children who contract measles before the age of 5, particularly under 2 years, and in those with compromised immune systems, such as those exposed to HIV [8,20]. Gender also plays a role, with boys being more frequently affected than girls, at a ratio of approximately 3:1 [3,20]. Genetic predispositions, including specific single-nucleotide polymorphisms, may influence susceptibility and disease progression, although the exact mechanisms remain unclear [1]. Despite

vaccination, some cases of SSPE have been reported, suggesting that early measles infection before vaccination can still lead to the disease [21,22]. The clinical presentation of SSPE includes cognitive decline, myoclonic seizures, and progressive neurological deterioration, often leading to a vegetative state [3,7]. Preventive strategies focus on enhancing measles vaccination coverage, which remains the most effective measure to reduce SSPE incidence globally[5,19].

Clinical manifestations in children. Subacute sclerosing panencephalitis (SSPE) is a progressive neurological disorder primarily affecting children and young adolescents, caused by a persistent infection of a mutated measles virus. The initial symptoms of SSPE often include subtle behavioral and intellectual deterioration, which can be easily overlooked or misdiagnosed. These early symptoms are typically followed by myoclonic jerks, seizures, and motor regression, with cognitive decline being a common feature across cases [3,23,24]. The disease progresses through several stages, with most children being diagnosed in stage II, characterized by more pronounced neurological symptoms such as myoclonic seizures and cognitive decline. As the disease advances, patients may experience vision loss, gait abnormalities, and eventually enter a vegetative state [3,7,25]. The clinical presentation of SSPE can vary significantly with age. In younger children, the disease may manifest rapidly, leading to severe neurological deterioration within months, as seen in cases of early onset SSPE[26]. In contrast, older children and adolescents may experience a more gradual progression, with a longer latency period between measles infection and the onset of SSPE symptoms [27,28]. Despite the variability in clinical presentation, common diagnostic features include elevated measles antibody titers in cerebrospinal fluid and characteristic EEG findings, such as periodic discharges [7,24]. The prognosis for SSPE remains poor, with most patients experiencing a progressive decline leading to death within a few years of diagnosis [6,28]. The disease is more prevalent in developing countries with lower measles vaccination rates, highlighting the importance of universal vaccination as a preventive measure [7,29].

Diagnostic methods. The diagnosis of Subacute Sclerosing Panencephalitis (SSPE) involves a multifaceted approach that integrates clinical assessment, laboratory and immunological markers, imaging techniques, EEG findings, and cerebrospinal fluid (CSF) analysis. Clinically, SSPE is characterized by progressive neurological symptoms such as behavioral changes, myoclonus, cognitive decline, and motor deterioration, which are categorized into four stages, from behavioral changes to a vegetative state [6,30]. Laboratory and immunological markers play a crucial role, with elevated anti-measles antibody titers in both serum and CSF being a hallmark of SSPE. The CSF also shows increased IgG levels and IgG index, which are critical for confirming the diagnosis [30–32]. Imaging techniques, particularly MRI, reveal abnormalities such as subcortical and periventricular white matter changes, cerebral atrophy, and basal ganglia involvement, which correlate with disease severity and progression [33,34]. Although MRI findings are diverse and may not always correlate with EEG or clinical features, they are essential for understanding the disease's progression [34]. EEG findings are distinctive, showing periodic high-voltage slow wave bursts, which are particularly characteristic in the early stages of the disease [30,35]. CSF analysis, besides confirming elevated measles antibodies, helps differentiate SSPE from other neurological disorders by examining protein electrophoretic patterns [32]. In cases where CSF studies are inconclusive, a brain biopsy may be necessary to detect inclusion bodies and measles virus antigens [36]. Overall, the integration of these diagnostic tools is vital for accurately diagnosing SSPE, guiding treatment, and understanding the disease's pathophysiology [6,36].

Immunological and paraclinical characteristics. Immunological abnormalities and immune responses play a critical role in influencing the prognosis of subacute sclerosing panencephalitis (SSPE), a progressive neurodegenerative disorder caused by a persistent measles virus infection. The pathogenesis of SSPE involves a complex interplay between viral persistence and host immune response, where immune dysregulation is a significant factor. Studies have shown that immune dysregulation, characterized by elevated levels of lymphocytes, B-cells, T-cells, and immunoglobulins such as IgG, IgM, and IgE, is prevalent in SSPE patients [37,38]. This dysregulation may lead to immune evasion by the virus and the initiation of autoimmune phenomena, contributing to the disease's progression [37]. The prognosis of SSPE is generally poor, with most patients experiencing rapid neurological decline despite treatment interventions such as intravenous immunoglobulins and antiviral therapies [39,40]. The immune response's role is further highlighted by the observation that genetically determined immune dysfunction can prevent effective cell-

mediated clearance of the measles virus, leading to a fulminant course of the disease [39]. Additionally, the presence of elevated anti-measles antibodies in the cerebrospinal fluid is a diagnostic marker for SSPE, indicating an ongoing immune response against the virus [35]. Despite these insights, effective treatments remain elusive, and the prognosis is often dismal, with most patients progressing to severe disability or death [40,41]. The correlation between immune parameters and clinical outcomes suggests that targeted immunomodulatory therapies could potentially improve prognosis, although further research is needed to validate these approaches [38]. Overall, the immune system's response to the persistent measles virus infection is a crucial determinant of SSPE's clinical course and outcome, underscoring the need for continued research into immunological interventions.

Treatment approaches. The management of Subacute Sclerosing Panencephalitis (SSPE), a progressive and often fatal neurological disorder caused by persistent measles virus infection, involves a combination of antiviral therapies, supportive care, and experimental approaches, each with varying degrees of effectiveness. Antiviral therapies such as ribavirin and interferon-alpha have shown promise in some cases. Ribavirin, particularly when administered intraventricularly, has been reported to achieve concentrations in the cerebrospinal fluid that inhibit SSPE virus replication, leading to clinical improvements in some patients [42–44]. Interferon-alpha, often used in combination with ribavirin, has demonstrated potential in slowing disease progression and improving neurological symptoms, especially when administered early in the disease course [43,45,46]. However, these treatments are not curative, and their efficacy can vary significantly among patients [47,48]. Supportive care remains crucial, focusing on managing symptoms and improving quality of life, as SSPE often leads to severe neurological decline [6,49]. Emerging treatments and experimental approaches, such as the use of inosiplex, have also been explored, but none have yet proven to be definitive solutions [47,49]. The prognosis for SSPE remains poor, with most patients experiencing a progressive decline leading to death within a few years of onset, although some cases have shown prolonged survival with intensive treatment [45,46]. The variability in treatment response underscores the need for further research to develop more effective therapies and to establish standardized treatment protocols [19,42].

Prevention strategies. Measles vaccination plays a crucial role in preventing subacute sclerosing panencephalitis (SSPE), a rare but fatal neurological complication of measles infection. Successful measles immunization programs have been shown to protect against SSPE, as the measles vaccine does not cause or accelerate SSPE, nor does it trigger the condition in individuals with a benign persistent wild measles infection [12]. Herd immunity is essential in controlling measles outbreaks and preventing SSPE, as it requires a population immunity level higher than 95% to effectively stop virus transmission [50,51]. Herd immunity not only protects vaccinated individuals but also provides indirect protection to those who cannot be vaccinated, such as infants and immunocompromised individuals [52,53]. However, achieving and maintaining herd immunity faces several barriers, including vaccine hesitancy fueled by misinformation and skepticism, which have led to declining vaccination rates in some regions [50,51]. Additionally, logistical challenges such as inadequate vaccination coverage, especially in developing countries with high birth rates, further complicate efforts to maintain herd immunity [54,55]. Mass vaccination campaigns, particularly those triggered by serosurveys or outbreaks, can help mitigate these challenges by targeting susceptible populations and preventing large-scale epidemics [56]. Effective communication strategies, including digital platforms, are vital to overcoming vaccine hesitancy and ensuring high vaccination coverage, thereby supporting the elimination of measles and SSPE [50]. Overall, while measles vaccination is a powerful tool in preventing SSPE and achieving herd immunity, addressing barriers such as misinformation and logistical challenges is critical for the success of vaccination campaigns.

Prognosis and outcomes in children. Subacute sclerosing panencephalitis (SSPE) is a rare, progressive, and fatal neurodegenerative disease resulting from a persistent measles virus infection, primarily affecting children and young adults. The survival rates for SSPE are generally poor, with many patients experiencing rapid neurological decline and death within a few years of diagnosis. In a study of 32 pediatric patients, 15.6% died, and 37.5% were bedridden, indicating severe disease progression and poor prognosis [3]. The disease often presents with myoclonic seizures, cognitive decline, and behavioral changes, with electroencephalogram (EEG) abnormalities being

a key diagnostic feature [23,57]. Quality of life (QoL) for children with SSPE and their families is significantly impacted due to the chronic and debilitating nature of the disease. The neurocognitive and psychosocial challenges associated with SSPE lead to a compromised QoL, similar to other neurocognitive developmental disorders. Families often face emotional and financial burdens, exacerbated by the need for long-term care and the progressive nature of the disease [58]. Long-term neurological complications of SSPE include persistent cognitive and motor deficits, which are compounded by the lack of effective curative treatments. Current therapeutic approaches, such as interferon alpha, inosine pranobex, and ribavirin, aim to prolong life and improve QoL, but they do not halt disease progression [49]. The disease's impact is more pronounced in developing countries where measles vaccination rates are lower, leading to higher SSPE incidence [23,57]. Overall, SSPE remains a devastating condition with significant implications for affected children and their families, underscoring the importance of measles vaccination and early diagnosis to mitigate its impact [59].

Challenges and future perspectives. Subacute sclerosing panencephalitis (SSPE) remains a poorly understood and challenging condition, with significant gaps in the understanding of its etiology, treatment, and prevention. The exact pathogenesis of SSPE is not fully elucidated, although it is known to result from a persistent infection with a mutated measles virus in the central nervous system. This mutation affects the viral genome, particularly the matrix gene, leading to a chronic infection that the immune system fails to clear effectively [1,60]. The disease predominantly affects children who contracted measles at a young age, especially under five years, and is more prevalent in regions with low vaccination rates [8,14]. Despite various therapeutic attempts, including the use of interferon-alpha and antiviral agents like ribavirin and isoprinosine, no curative treatment exists. These therapies have shown only limited success in stabilizing or modestly improving the condition, and their efficacy is often hampered by the invasive nature of administration and high costs, particularly in resource-limited settings [48,61,62]. The phenomenon of spontaneous remission in a small percentage of patients further complicates the assessment of treatment efficacy [61,63]. Prevention through vaccination remains the most effective strategy, yet recent declines in vaccination rates, exacerbated by the COVID-19 pandemic, have led to an increase in SSPE cases [5,64]. Future research should focus on understanding the immunogenetic factors that contribute to SSPE susceptibility and progression, developing more accessible and effective therapeutic regimens, and enhancing global vaccination efforts to prevent measles infections that could lead to SSPE [1,8,14]. Additionally, there is a need for improved diagnostic tools to facilitate early detection and intervention, potentially altering the disease course [60,62].

Conclusion. The comprehensive analysis of SSPE highlights its devastating impact on affected children and adolescents. The persistent challenges in treatment, combined with the resurgence of SSPE due to reduced vaccination coverage, underscore the need for reinforced immunization campaigns and innovative therapeutic strategies. Future research must focus on unraveling the immune mechanisms behind SSPE and developing targeted treatment options. Addressing vaccine hesitancy and ensuring global vaccine equity are pivotal in the fight against this fatal disease.

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