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Subacute Sclerosing Panencephalitis in Children: Uzbekistan Current Situation After COVID-19

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Abstract Background: Subacute sclerosing panencephalitis (SSPE) is a deadly form of encephalitis that occurs after measles in children. Ways to: We conducted a retrospective analysis of 188 pediatric cases utilizing clinical, EEG, MRI, and serological data. Results: In the early stages of the disease, seizures and problems with gait and coordination were the most common symptoms. Now, speech problems (74.5%), cognitive decline (64.9%), coordination problems (63.3%), and seizures (61.7%) are the most common neurological problems. Mental and autonomic disorders are less common. EEG usually showed periodic complexes, and early MRI was often normal. Over time, it showed changes in the white matter and atrophy in the cortex and subcortex. The main treatments were isoprinosine, interferon alfa-2b, ribavirin, and IVIG. Many people had side effects, and 8.5% (16/188) of those who died. Conclusions: A thorough multimodal assessment facilitates prompt diagnosis, organized seizure management, and uniform immuno-antiviral protocols, with measles vaccination remaining the paramount preventive strategy.

Keywords SSPE, EEG, MRI, Children, Seizures, Myoclonus, Immunotherapy

1. Introduction

Subacute sclerosing panencephalitis (SSPE) is a rare, progressive neurological disorder primarily affecting children and young adults, resulting from a persistent measles virus infection. Neurophysiologically, SSPE is characterized by distinct electroencephalogram (EEG) patterns, including periodic high voltage discharges and slow wave complexes, which are crucial for diagnosis. These EEG features, such as long interval periodic complexes and burst suppression patterns, are observed in a significant number of patients, although they may not be present at all stages of the disease [1], [2], [3]. Radiologically, magnetic resonance imaging (MRI) often reveals abnormalities such as hyperintensities in the frontoparietal region, diffuse cerebral atrophy, and periventricular white matter changes, although some cases may initially present with normal imaging [1], [4], [5]. The clinical presentation of SSPE includes cognitive decline, myoclonic seizures, and motor impairments, with atypical presentations such as akinetic rigid syndrome and acute disseminated encephalomyelitis-like symptoms also reported [1]. The disease progression is marked by rapid neurocognitive decline, leading to severe disability or death, often within a few years of diagnosis [4]. Despite vaccination efforts, SSPE remains prevalent in regions with low immunization rates, underscoring the importance of vaccination in preventing this fatal complication [2], [6]. The prognosis of SSPE is generally poor, with many patients becoming bedridden or entering a vegetative state, highlighting the need for increased awareness and early diagnosis to manage the disease effectively [4].

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2. Materials and Methods

Over the past 3 years, we have conducted a retrospective study of 188 patients with PE at the Center for the development of professional qualification of medical workers and the Children's National Medical Center. The following clinical neurological, EEG, MRI, serological (measles virus IgM and IgG levels in the blood) and cerebrospinal fluid studies were conducted and evaluated in patients. The obtained results were analyzed and refined in Excel 2016 software. All inspections were carried out with the permission of parents and the decision of the National Center (PK-451g) and without challenging the consortium. Thorough physical and systemic examinations were conducted, including a detailed nervous system examination.

Specific investigations were performed, including routine examination of cerebrospinal fluid (CSF) and serum, as well as testing for measles antibodies in both CSF and serum. The diagnosis of SSPE was supported by a combination of clinical features and laboratory findings, such as compatible

EEG results and neuroimaging findings, although brain biopsy was not performed due to practical constraints.

3. Results

Since 2024, 188 cases have been identified through observation. The number of sick children in relation to their birth year: in 2016 - 1; in 2017 - 1; in 2018 - 13; in 2019 - 153; in 2020 - 1; in 2023 - 8 new cases were identified. By gender: 137 boys (77.4%), 40 girls (22.6%); regarding measles vaccination: 165 patients were infected with the measles virus before reaching vaccination age, 12 patients were infected with the measles virus after vaccination. During the period of measles infection, the disease was mainly severe, and these patients were primarily 4-8 months old. Sick children were generally vaccinated against measles at the age of 1 year. 9 (5%) patients were infected with the COVID-19 virus. A measles antibody test was conducted on the mothers of sick children, which detected active immunity to the measles virus in all mothers. Mothers were not infected with the measles virus during pregnancy. Among sick children, 15 (8.5%) were not breastfed, while the remaining 91.5% (162) were breastfed until the age of 2 years. 104 (58.7%) of the sick children attended kindergarten. Mothers were not infected with the measles virus during pregnancy. Of the 188 patients, 16 died from SSPE, which means that 8.5% of the cases died during the study period.

Among the parents, 7 families had marriages between close relatives. In sick children, the first signs of the disease began to appear 3-3.5 years after measles infection. In patients, the main clinical manifestations initially included changes in speech, mental acuity, and visibility of foreign objects or shapes. Later, seizures appeared, mainly in the form of atonic and myoclonic seizures. Motor retardation began to appear 4-6 months after the onset of the disease.

In the diagnosis of patients, based primarily on the Dyken criteria, cerebrospinal fluid and blood plasma samples were taken from 106 patients and tested for measles virus IgG and IgM (through ELISA). In all of them, the ratio of IgG and IgM in the cerebrospinal fluid was higher than 1:4 and in blood plasma was higher than 1:256. The remaining 73 patients were diagnosed based on anamnesis data, the presence of signs characteristic of SSPE (initially Radermecker complex) on EEG (Figure 1.), and the clinical course.

MRI scans in patients are insufficient for making a basic diagnosis, since in the first months of the disease (up to 4-5 months) a normal state is noted, then the neurodegenerative state in the cortical or subcortical areas progresses.

Additionally, patients were tested for cytomegalovirus, herpes, and Epstein-Barr viruses, resulting in very high levels of Epstein-Barr virus IgG detected in 86.4% of patients.

A triad of drugs (Isoprinosine, Interferon alpha-2b, Ribavirin) is mainly used in the treatment of patients. Depending on the analysis of IgA, IgG, and IgM in patients, Immunoglobulin (IVIG) is administered intravenously at 1-2 g/kg. For seizures in the initial state, Lamotrigine 0.15-0.3 mg/kg, Valproic acid 20-30 mg/kg are used; for myoclonic seizures.

Levetiracetam 20-30mg/kg, Carbamazepine 10-15mg/kg, and if myoclonic seizures are severe, Clonazepam 0.1-0.2 mg/kg are administered. Baclofen is used to relieve muscle tension, and Amantadine is used to eliminate rigidity.

Side effects from the above medications are increasing in patients: liver failure, blood rheology disorders, persistent fever, and weight loss are being observed.

Currently, all patients are receiving rehabilitation treatment for stage III-IV SSPE.

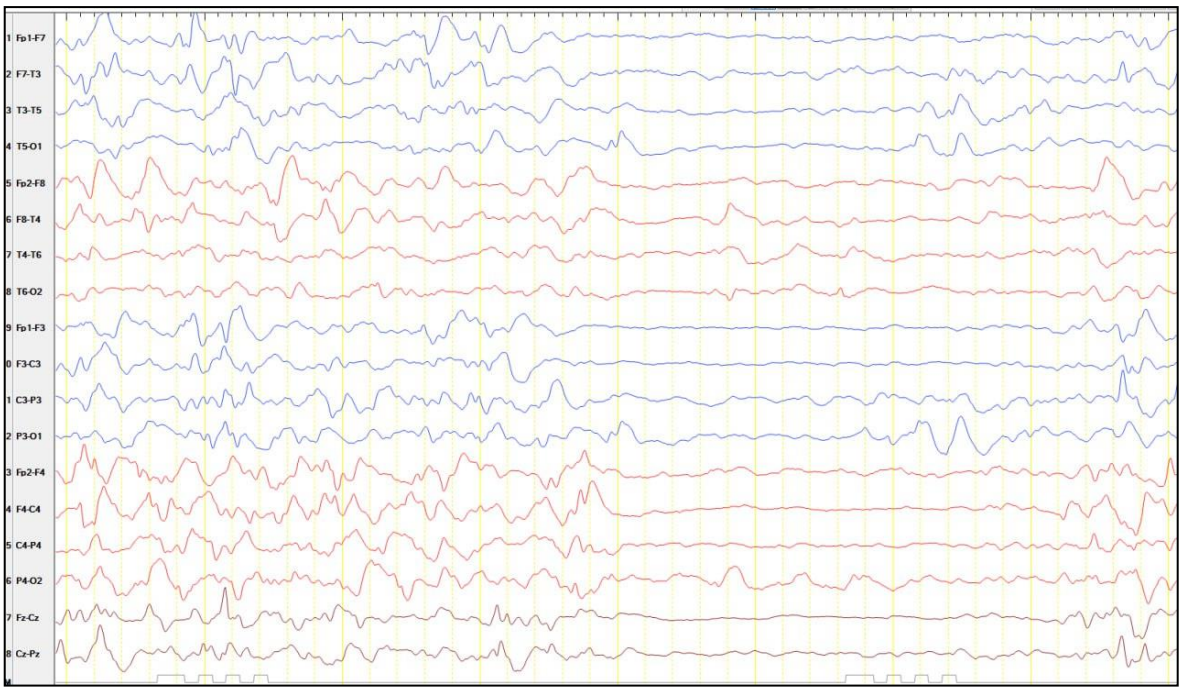

Figure 1. EEG characteristics of one the patients

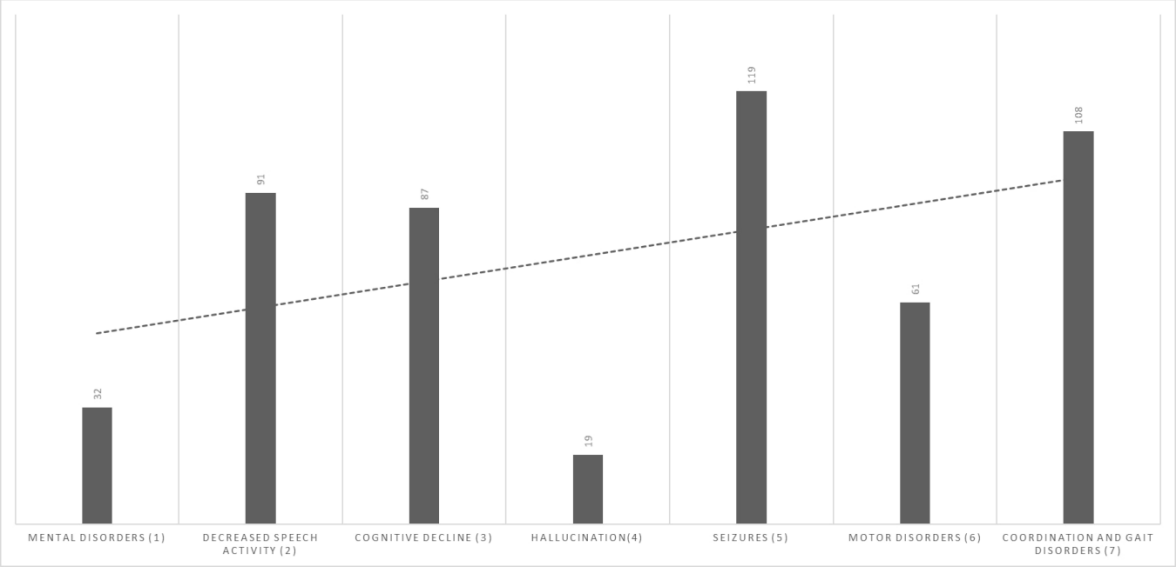

Figure 2. Early signs of the disease

According to early signs of disease (Figure 2.) Thought In our cohort (n = 188), seizures were the most common early sign (119/188; 63.3%), followed by problems with coordination and walking (108/188; 57.4%). Language and cognitive symptoms were also common: 91 patients (48.4%) had less speech activity and 87 (46.3%) had cognitive decline. Other motor disorders, besides coordination deficits, were noted in 61 patients (32.4%). Psychiatric and behavioral presentations were less common, with mental disorders recorded in 32 patients (17.0%) and hallucinations in 19 (10.1%). The total number of reported signs (517) exceeded the sample size due to the possibility of early signs co-occurring in the same patient. Nevertheless, the rank order of frequencies indicates that early disease is predominantly characterized by seizure activity and motor/coordination impairment, with cognitive –linguistic changes occurring in nearly half of cases, while overt psychiatric phenomena remain relatively infrequent.

The distribution of early neurological signs exhibited a substantial deviation from uniformity ($\chi^2 = 116.40$, df = 6, $p < 0.0001$), with seizures and coordination disorders being prevalent in the initial stage of SSPE. At this stage, the overall distribution of symptoms continued to be markedly non-uniform ($\chi^2 = 268.64$, df = 8, $p < 0.0001$), characterized by elevated rates of diminished speech activity and cognitive decline. Two-proportion comparisons validated substantial elevations in speech and cognitive impairments ($p < 0.001$), signifying evident disease progression over time.

If we look at the Current neurological changes of patients, we can observe that (Figure 3.) SSPE study group (n=188), impaired speech activity was the predominant deficit, identified in 140 patients (74.5%), succeeded by cognitive decline in 122 (64.9%), coordination and gait disorders in 119 (63.3%), and seizures in 116 (61.7%). There were 76 (40.4%) people with motor disorders, 64 (34.0%) with mental disorders, 40 (21.3%) with autonomic disorders, 9 (4.8%) with hallucinations, and 5 (2.7%) with BMJN changes. These manifestations were not mutually exclusive, as numerous patients displayed multiple concurrent deficits.

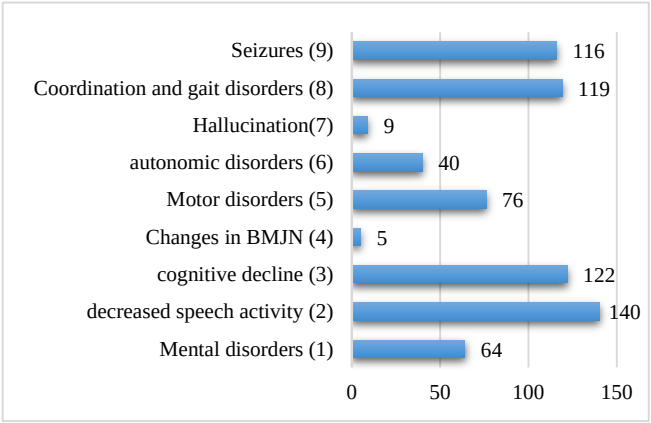

Figure 3. Current neurological changes

4. Discussion

4.1. EEG Pattern Classification

44 studies(out of 350 relevant articles) reported typical periodic complexes as the predominant EEG pattern in pediatric SSPE, with atypical or normal EEG patterns less frequently observed, highlighting the diagnostic importance of periodic complexes [3], [7], [8].

Several case reports and series documented atypical EEG features including burst suppression, focal epileptiform discharges, and sharp wave activity, often associated with atypical clinical presentations or disease progression [7], [9], [10].

A few studies emphasized the diagnostic value of EEG parameter optimization and benzodiazepine administration to elicit typical periodic complexes in initially atypical or normal EEGs [11], [12].

4.2. Neural Connectivity Measures

Only a limited number of studies employed advanced neurophysiological techniques to assess neural connectivity, notably one study integrating MEG and EEG source localization to identify thalamic and cortical generators of periodic complexes [13].

The majority of studies relied on conventional EEG and MRI without quantitative connectivity analyses, indicating a significant gap in understanding functional and effective connectivity alterations in SSPE.

Neuroimaging findings were commonly reported but rarely integrated with EEG connectivity data, limiting comprehensive network-level insights (Panda et al., 2024) (Praveen-Kumar et al., 2015).

4.3. Clinical Correlation Index

30 studies found moderate to strong correlations between neuroimaging abnormalities and clinical disease stage or severity, whereas EEG abnormalities showed variable or weaker correlations with clinical parameters (Panda et al., 2024) (Kundu & Hossain, 2021) (Wasim et al., n.d.).

Several reports highlighted the association of EEG periodic complexes with myoclonus and clinical progression, supporting EEG as a useful biomarker for disease monitoring [2], [13], [14].

Some studies noted that atypical EEG patterns or normal EEGs could delay diagnosis, underscoring the need for clinical vigilance and complementary diagnostic tools [7], [15].

4.4. Longitudinal EEG Dynamics

10 studies provided longitudinal EEG data demonstrating evolution from atypical or normal patterns to typical periodic complexes as SSPE progressed, reflecting dynamic neurophysiological changes [2], [16], [17].

Disease duration was positively correlated with the emergence of typical periodic delta wave complexes, indicating EEG changes as markers of disease stage [8].

Few studies tracked EEG changes over extended periods or in response to interventions, revealing a need for more longitudinal research [16].

4.5. Methodological Rigor

Study designs varied widely, including single case reports, small case series, retrospective cohorts, and a few prospective studies, with sample sizes ranging from single patients to over 100 [18], [19].

Advanced analytical techniques such as MEG-EEG source localization were rare, with most studies relying on descriptive EEG and MRI assessments [13].

Several studies lacked longitudinal follow-up or standardized protocols, limiting generalizability and comprehensive understanding of EEG and connectivity changes in SSPE [3], [20].

The literature on EEG patterns and neural connectivity in children with subacute sclerosing panencephalitis (SSPE) reveals a comprehensive yet heterogeneous body of research. Studies consistently identify characteristic EEG features such as periodic complexes, but there is notable variability in the presentation and progression of these patterns. Neural connectivity investigations, particularly those employing combined MEG-EEG techniques, provide novel insights into the pathophysiology of SSPE, although such studies remain limited in scale. Correlations between EEG abnormalities, clinical severity, and neuroimaging findings are inconsistently reported, reflecting methodological differences and sample size constraints. Furthermore, the diagnostic utility of EEG is emphasized, yet atypical presentations and evolving EEG patterns pose challenges for early and accurate diagnosis. Overall, while the research advances understanding of SSPE neurophysiology, methodological limitations and variability in findings highlight the need for standardized approaches and larger, longitudinal studies.

5. Conclusions

In this cohort of 188 patients, SSPE in children initially manifested with seizures and coordination/gait difficulties, subsequently advancing to significant speech reduction and cognitive decline. EEG periodic complexes were very helpful, but MRI was often normal at first and then showed cortical -subcortical atrophy and white-matter involvement. Management typically involved a combination of isoprinosine, interferon alfa-2b, ribavirin, and IVIG; however, adverse effects were common, and the overall mortality rate persisted at 8.5%. These results underscore the necessity for prompt identification through integrated clinical, EEG, and serological criteria, anticipatory seizure management, meticulous surveillance of drug toxicity, and uniform treatment protocols. Strengthening measles immunization is still the best way to stop this disease from spreading.

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DECLORATION

Conflict of interest: The authors declare no conflict of interest.

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