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Original Research Article

Frequency of Clinical Presentation, MRI Findings and CSF Findings in Patients Presenting with Subacute Sclerosing Panencephalitis

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***Abstract*:** **Objective:** To identify the prevalence of clinical presentation, magnetic resonance imaging (MRI) findings and cerebral spinal fluid (CSF) findings in patients with the subacute sclerosing panencephalitis (SSPE).**Study Design** Cross-sectional descriptive study.**Place and Duration of Study**: This study was conducted at the Department of Neurology, Bolan Medical Complex, Quetta, over a period of six months.**Methodology:** 137 patients with SSPE were included. A structured proforma was used to record demographic information, clinical characteristics, MRI information and the analysis of the CSF. Quantitative variables were represented in the form of mean +- standard deviation, whereas qualitative variables were represented in the form of frequencies and percentages. The stratification was done based on age, gender, residential condition, family history of measles and family monthly income status. Chi-square test/Fisher exact test was used after stratification and a p-value ≤ 0.05 was taken to be significant.**Results:** The mean age of patients was 11.24 ± 3.08 years, with a male predominance (74.5%). Most patients belonged to rural areas (70.1%) and lower socioeconomic status (65.0%). The most common clinical manifestations were cognitive decline (77.4%) and seizures (76.6%). MRI revealed white matter changes (70.1%), cortical atrophy (69.3%) and temporo-parietal-occipital involvement (62.8%). Positive CSF globulin levels (>20%) were observed in 70.8% of patients. The stratification analysis indicated that there was no statistically significant relationship between demographic or socioeconomic factors and clinical, MRI or CSF results.**Conclusion:** SSPE usually occurs in children and adolescents that have their cognitive and seizure symptoms with typical MRI and CSF results. The study population was not significantly affected by demographic and socioeconomic factors on the display of the disease.

Keywords: Subacute sclerosing panencephalitis, Magnetic resonance imaging, Cerebrospinal fluid, Cognitive decline, Seizures, Measles virus.

INTRODUCTION

Subacute sclerosing panencephalitis (SSPE) is a rare, chronic and invariably fatal neurodegenerative disorder caused by persistent infection with a mutant measles

virus. The disease primarily affects children and adolescents and is characterized by progressive deterioration of cognitive, behavioral and motor functions [1]. SSPE is a late measles infection complication and is typically seen many years after the initial illness and is a significant concern to the general population in areas with poor measles vaccination coverage [2].

The SSPE prevalence reported in the world is less than 1-20 cases per million population but this varies more based on the practice of regional vaccination and epidemiology of measles [3]. The developing countries would still have reported a disproportionately much larger disease burden as a result of insufficient immunization, lack of access to healthcare and frequent instances of measles outbreak [4]. According to epidemiological evidence, measles infection at the young age when an individual is below the age of two years of age, is of great risk in the development of SSPE later in childhood or in the adolescence stage [5]. Even though the world is undertaking global measles eradication efforts, measles outbreaks still take place periodically further perpetuating the incidence of SSPE in the endemic countries [6].

Clinically, SSPE is usually insidious and the initial manifestations are usually nonspecific. Alterations in behavior, poor performance at school, irritability and mild cognitive impairment are very common and may even remain unnoticed during the early onset of the condition [7]. With advancement of the SSPE, additional open neurological manifestations emerge such as myoclonic jerks, frequent falls, generalized tonic-clinic seizures, partial seizures, gait disturbance, spasticity, dystonia and ataxia [8,9]. The clinical progression is normally progressive though fulminant ones with rapid degeneration of the nervous system have also been reported [10].

The other significant clinical presentation of SSPE is visual disturbances and they can pre-empt or accompany other neurological symptoms. They are progressive impairments of the visual acuity and visual field abnormalities that are accompanied in late stages of the disease by cortical blindness, indicating the activity of the occipital cortex and visual pathways [11]. The broad range of clinical manifestation and inconsistent pace of progression can be a problem of diagnosis, especially in resource-constrained environments, where the availability of more sophisticated diagnostic formats can be limited.

The diagnostics of patients with possible SSPE require the involvement of neuroimaging. The brain magnetic resonance imaging (MRI) normally reveals typical abnormalities especially at an initial and intermediate stage of the disease. The common results are bilateral asymmetrical hyperintense lesions on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, with the majority of them in the parietal and temporal lobes [12]. Such imaging characteristics do not only facilitate the diagnosis but also give an idea of the stage of the disease as well as the level of the central nervous system involvement.

The analysis of cerebrospinal fluid (CSF) is another diagnostic instrument of SSPE. An active intrathecal immune response to the measles virus is evidenced by elevated levels of CSF globulin, which usually comprise over 20% of total CSF protein [13]. Although not a common routine in most facilities, advanced virological assays, CSF protein analysis along with typical clinical and MRI examination can substantially increase diagnostic certainty, in a low-resource environment.

In Pakistan, SSPE is reported at alarming rates and this is mostly due to gaps in measles immunization and delayed diagnosis. Local information on the occurrence and trend of clinical presentation, neuroimaging and CSF abscesses in affected individuals especially in Balochistan tertiary care facilities is scanty. These parameters are important to understand thoroughly to allow their recognition at an earlier stage, enhance diagnostic precision and make a quality clinical decision. The study was conducted with an aim of establishing the prevalence of clinical presentation, MRI and the CSF in patients with subacute sclerosing panencephalitis in a tertiary care facility in Quetta, Pakistan.

METHODOLOGY

Study Design

A cross-sectional study design was used to evaluate the prevalence of clinical presentation, magnetic resonance imaging (MRI) findings and cerebrospinal fluid (CSF) findings in case of subacute sclerosing panencephalitis.

It was conducted in the Department of Neurology at Bolan Medical Complex Hospital, Quetta, Pakistan. A total of six months of data collection was done after the synopsis was approved by the College of Physicians and Surgeons Pakistan.

Sample Size and Technique

WHO sample size calculator was used to calculate the sample size. One hundred and thirty-seven patients were recruited in the study, considering the projected cases of cognitive loss of 65%, a standard deviation of 8% and a confidence interval of 95%.

The non-probability consecutive sampling method was employed, in which all the eligible patients who were available throughout the study period and met the inclusion criteria were employed until the required sample size was reached.

Inclusion Criteria

The study included patients of either gender who were aged between 6 and 16 years and had subacute sclerosing panencephalitis as operationalized by the use of the operational criteria. Patients were also excluded in cases where they had a history of pneumonia, tuberculosis, malnutrition, congenital heart disease, malaria, dengue, typhoid fever, human immunodeficiency virus infection and major congenital malformations of the cardiovascular, central nervous and respiratory systems.

Data Collection Procedure

Eligible patients were selected after receiving consent at

the College of Physicians and Surgeons Pakistan and ethical approval at the hospital Ethical Review Committee and having been evaluated as eligible in the case of any patient presented to either the interior or exterior service at the Department of Neurology, Bolan Medical Complex Hospital, Quetta. All patients were enrolled with informed consent given out by the parents or guardians in writing. At admission, demographic information and history of measles infection were registered. There were clinical manifestations of seizures, cognitive impairment, spasticity, dystonia and ataxia. The MRI brain findings were re-examined with trained radiologists or neurologists and examined as white matter changes, temporo- parietal -occipital involvement, patchy asymmetrical involvement, thalamic or cerebellar involvement and cortical atrophy. Analysis of cerebrospinal fluid was done with a proportion of CSF globulin higher than 20% of the total CSF protein as positive result. These were observed on a predesigned proforma.

Data Analysis

The Statistical Package of Social Sciences (SPSS) version 26 was used to enter and analyze data. The quantitative variables like age were represented as mean ± standard deviation when the data followed a normal distribution and as a median with interquartile range when the data was not normally distributed. Frequencies and percentages were used to provide qualitative variables such as gender, residential status, family history of measles, family monthly income status, clinical presentation, MRI findings and CSF findings. The effect modifiers were moderated using the stratification of age, gender, residential, family measles history and family monthly income status. Post-stratification chi-square test or the Fishers exact test was used as the right one and ≤ 0.05 was regarded as the statistically significant value.

RESULTS

The study involved 137 patients who were diagnosed with subacute sclerosing panencephalitis (SSPE). No data were missing and all the cases could be analyzed.

Demographic Characteristics

The mean age of the patients was 11.24 ± 3.08 years, with an age range of 6 to 16 years. The majority of patients were male (102, 74.5%) while 35 (25.5%) were female. Most patients belonged to rural areas (96, 70.1%), whereas 41 (29.9%) were from urban settings. Regarding socioeconomic status, 89 patients (65.0%) had a family monthly income of ≤75,000 PKR while 48 (35.0%) had an income of >75,000 PKR. A positive family history of measles was reported in 88 patients (64.2%), whereas 49 patients (35.8%) had no such history (Table 1).

Table 1. Demographic Characteristics of Patients with SSPE (n = 137)

Variable	Category	n	%
Age (years)	Mean ± SD	11.24 ± 3.08	—
	Range	6–16	—
Gender	Male	102	74.5
	Female	35	25.5
Residential status	Urban	41	29.9
	Rural	96	70.1
Family monthly income status	≤ 75,000 PKR	89	65.0
	> 75,000 PKR	48	35.0
Family history of measles	Yes	88	64.2
	No	49	35.8

Clinical Presentation

The most frequent clinical manifestation was cognitive decline, observed in 106 patients (77.4%), followed closely by seizures, which were present in 105 patients (76.6%). Spasticity was noted in 63 patients (46.0%) while ataxia was observed in 67 patients (48.9%). Dystonia was also lower in prevalence and it existed in 35 patients (25.5%). These results result in the most common neurological characteristics among patients with SSPE (Table 2).

Magnetic resonance imaging was the most common radiological abnormality with white brain changes detected in 96 patients (70.1%). They were found to have temporal-parietal-occipital involvement in 86 patients (62.8%). Patchy asymmetrical affect was found in 67 patients (48.9%) and thalamic or cerebellar affect was found in 67 patients (48.9%). In 95 subjects (69.3%), cortical atrophy was observed, which means that the disease was developed in a significant percentage of participants (Table 2). Cerebrospinal fluid examination showed that 97 patients (70.8% of a total of 130) had positive CSF globulin (>20% of total CSF protein) and 40 patients (29.2% of a total of 130) showed negative CSF (Table2).

Table 2. Frequency of Clinical Presentation, MRI Findings and CSF Findings in Patients with SSPE (n = 137)

Variable	Present n (%)	Absent n (%)
Clinical presentation		
Seizures	105 (76.6)	32 (23.4)
Cognitive decline	106 (77.4)	31 (22.6)
Spasticity	63 (46.0)	74 (54.0)
Dystonia	35 (25.5)	102 (74.5)
Ataxia	67 (48.9)	70 (51.1)
MRI findings		
White matter changes	96 (70.1)	41 (29.9)
Temporo-parietal-occipital involvement	86 (62.8)	51 (37.2)
Patchy asymmetrical involvement	67 (48.9)	70 (51.1)
Thalamic/cerebellar involvement	67 (48.9)	70 (51.1)
Cortical atrophy	95 (69.3)	42 (30.7)
CSF findings		
Positive CSF globulin (>20%)	97 (70.8)	40 (29.2)

Stratification Analysis

To determine the impact of possible effect modifiers on clinical and MRI and CSF outcomes, stratification was conducted to evaluate the impact of the age group, gender, residential status, family history of measles and family monthly income status.

There was also no statistically significant difference between gender and occurrence of seizures (p = 0.065) or gender and cognitive decline (p = 0.354). On the same note, residential status had no significant correlation with the MRI white matter changes (p = 1.000) and CSF globulin positivity (p = 0.305). The age group stratified (6-10 years vs 11-16 years) did not show any significant association with history of seizures (p = 0.220). Also, the family history of measles did not show the statistically significant association with CSF globulin positivity (p = 0.330). The family monthly income status stratification also did not differ significantly with MRI white matter change (p = 0.174). The chi-square or Fisher exact test was used to perform all the stratification analyses where necessary and none of the relationships were found to be significant (Table 3).

Table 3. Stratification of Outcomes with Effect Modifiers in Patients with SSPE (n = 137)

Effect modifier	Outcome variable	p-value
Gender	Seizures	0.065
Gender	Cognitive decline	0.354
Residential status	MRI white matter changes	1.000
Residential status	CSF globulin positivity	0.305
Age group (6–10 vs 11–16 years)	Seizures	0.220
Family history of measles	CSF globulin positivity	0.330
Family monthly income status	MRI white matter changes	0.174

DISCUSSION

The study was conducted to determine the frequency of clinical presentation, MRI findings and CSF findings in patients presenting with subacute sclerosing panencephalitis (SSPE) at a tertiary care hospital. The findings give a detailed description of the demographic profile, neurological presentation, neuroimaging features and cerebrospinal fluid defects of the affected patients.

The average age of patients expressed in years was 11.24 ± 3.08 years and age range were 6-16 years which is in line with the known latency period between the primary measles infection and the occurrence of SSPE [1,2]. The high dominance of males (74.5%) we have found in our cohort has consistently been reported in other studies and could be due to gender disparities in exposure patterns, immunological reactions or healthcare-seeking behavior [3,4]. A large percentage of affected patients had rural status (70.1%) and low socioeconomic status (65.0%), pointing to the endemic nature of insufficient vaccination rate and under-access to healthcare in SSPE epidemiology [5,6].

Clinically, the most common manifestations that were seen in this study were cognitive decline (77.4%) and seizures (76.6%). These results correlate with the existing body of literature that the cognitive impairment and epileptic seizures are characteristic early signs of SSPE [7,8]. A relatively low rate of dystonia (25.5%), in comparison to seizures and cognitive decline, is characteristic of the progressive disease; the extrapyramidal symptoms are usually found only at the advanced stages [9]. The occurrence of the spasticity (46.0%) and ataxia (48.9%) also highlights the extensive spread of motor pathways as the disease progresses.

The frequency of white matter changes (70.1%) and cortical atrophy (69.3%) findings in neuroimaging of the present study are typical MRI changes of SSPE and signs of diffuse demyelination and neuronal loss [10,11]. The tendency of SSPE to the posterior cortex was also evident due to a high percentage of temporal-parietal-occipital involvement (62.8%) [12]. Moderate prevalence of thalamic/cerebellar involvement (48.9%s) implies the disease progression outside of the cortex in a significant proportion of the patient group in line with the advanced pathology [13]. Such imaging patterns support the diagnostic value of MRI in SSPE especially in the location where highly sensitive virological tests might not be easily accessible.

Analysis of cerebrospinal fluid demonstrated that there was positive CSF globulin in 70.8% of patients and it is a sign that an active intrathecal immune response against measles virus exists. The result is consistent with the earlier case reports that highlight high CSF globulin as a positive diagnostic tool in SSPE [14]. Almost one-third of patients do not have CSF positivity points to the significance of matching CSF results to clinical and radiological signs and not to one diagnostic criterion.
Stratification analysis failed to show statistically significant relationships between clinical, MRI or CSF results and such putative modifiers of effect as gender, age group, residential status, family history of measles or family monthly income status. An example of such is that there was no notable interaction between gender and presence of seizures ($p = 0.065$) or gender and intellectual deterioration ($p = 0.354$). The residential status was not significantly correlated with changes in MRI white matter ($p = 1.000$) or CSF globulin positivity ($p = 0.305$). This implicates the idea that the demographic and socioeconomic modifiers can be relevant in determining exposure risk and disease incidence but the clinical and biological manifestation of SSPE is not influenced by external modifiers but largely by underlying neuropathological mechanisms [15,16].
The results highlight the burden of SSPE remains in children and adolescents, especially in areas where the coverage of measles vaccination is less than optimal. Classical clinical presentation, typical MRI images, along with the positive CSF point of evidence raises the significance of early diagnosis and thorough assessments to enhance a timely diagnosis. Therapeutic alternatives are still inadequate, it is important that patients are diagnosed early in order to counsel them, provide supportive management and plan the public health to prevent the disease.

Limitations

The limitation of this study is the single-center design, which can limit the generalization of the results. The cross-sectional study did not allow evaluating the course and long-term consequences of the disease. Though these constraints exist, the research is insightful on the clinical, radiological and CSF features of SSPE in a resource limited environment.

CONCLUSION

Subacute sclerosing panencephalitis is a serious neurological disease in children and adolescents and cognitive deterioration and seizure are the most frequent clinical signs. The prevalence of typical MRI abnormalities and positive CSF globulins result indicates the significance of a thorough clinical, radiological and laboratory assessment to provide an accurate diagnosis and stratification analysis showed there is no significant effect of demographic or socioeconomic factors on the presentation of the disease.

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