ORIGINAL ARTICLE

Predictors of Clinical Course of Subacute Sclerosing Panencephalitis: Experience at the Children's Hospital, Lahore

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ABSTRACT

Objective: To determine the clinical course of Subacute Sclerosing Panencephalitis (SSPE) and different factors affecting the clinical course.

Study Design: Descriptive study.

Place and Duration of Study: The Children's Hospital, Lahore, from October 2005 to May 2008.

Methodology: All serologically confirmed patients of SSPE were registered and clinical staging of these patients were done from stage-I to stage-IV. Clinical course of these patients was classified by using neurological disability index as fulminant, acute, subacute, and chronic course. Clinical course was analyzed for any difference with age, gender, immunization for measles, measles infection, nutritional status and correlation with age of onset of SSPE, (Spearman's correlation), using statistic package for social science (SPSS) V. 14.

Results: A total of 57 cases (41 males, 16 females) with mean age of 7.45 years were studied. Forty (71.4%) of them were vaccinated with single dose at about 9 months of age, 41% (23/57) had measles infections ≤ 2 years of age. Using the Neurology Disability Index for these patients 10.5% had fulminant, 17.5% had acute, 49.2% subacute and 22.8% had chronic course. Age, gender, age at measles infection, SSPE onset age and nutritional status were poor predictors of clinical course of SSPE. Unvaccinated patients showed significantly more rapid course of disease ($p = 0.04$).

Conclusion: Clinical course of SSPE cannot be predicted at the onset of this catastrophic disorder. Children not immunized against measles had a significant rapid course of disease.

Key words: *Subacute sclerosing panencephalitis. Neurological disability index. Immunization. Predictors. Clinical course.*

INTRODUCTION

Subacute Sclerosing Panencephalitis (SSPE) is a progressive inflammatory disease of central nervous system caused by a persistent, aberrant measles virus infection.[1] The annual incidence in the developing countries is high and quite variable because of high proportion of the total population below 2 years of age, a high proportion of the measles infection in very young age, more frequent sub-clinical measles virus infection and perhaps other host factor. The worldwide prevalence of SSPE is 0.04-21 per million population.[2] In Pakistan the annual induced rate is reported to be as high as 10 per million population.[3]

The latent period between measles infection and SSPE is around 4-6 years in most of the cases, but may range between 3 months to 18 years. Approximately 10% of cases have a fulminant course and occurrence of death within few months after onset, another 10% have far more prolonged clinical course ranging from 4 to 10 years after the onset of this disease.[1] SSPE is a disease which now appears to have altered epidemiological and clinical expression. Such changes have occurred in both developing and developed nations and that they may be due in some fashion to the effects of immunization or to a continued alteration in the virus itself and changing its mode of operation with new expression.[4] Same genotype of the virus may produce classical SSPE in some patients and fulminant SSPE in other patients.[5]

The disease still continues to take lives of children in the developing world and its uncommon modes of presentations pose diagnostic difficulties. Early diagnosis and true clinical staging SSPE is not always easy. A high index of suspicion is needed to detect SSPE in its typical, atypical and rare manifestations. Although SSPE is an invariably fatal disease, studies about the treatment of SSPE demonstrate that the early initiation of the treatment slows the progression and improves patient's quality of life.[6]

This study was conducted to evaluate the clinical course and its correlation with various factors of the confirmed SSPE patients admitted in the Neurology Department.

METHODOLOGY

All children with diagnosed SSPE admitted in the Paediatric Neurology Department, The Children's Hospital, Lahore, from October 2005 to March 2008 were enrolled in the study. The diagnosis of SSPE was based on the guidelines of the international SSPE consortium and consisted of two major criteria; typical or

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atypical course and elevated serum measles specific antibody titers and at least one minor criterion, classical EEG with periodic slow wave complex or elevated cerebrospinal fluid (CSF) measles – specific – antibody.[7] Demographic profile was recorded including age, gender and nutritional status. Age of onset of symptoms, history of immunization against measles, age at time of vaccination, history of development of measles rash and age of contracting measles were documented. SSPE disease was divided in 4 stages as follows; stage-I = behavioral, cognitive, personality changes and myoclonic spasms; stage-II = further mental behavior deterioration, myoclonic seizures generalized and more frequent myoclonic spasm, apraxias, agnosias and extra pyramidal motor signs; stage-III = visual difficulties, no independent ambulation, generalized myoclonic seizures, frequent and with long durations myoclonic spasm, no spontaneous speech, may be blind, bed ridden, dysphasic and movement disorders may appear, and stage-IV = no myoclonic spasms, low voltage EEG, neurovegetative states.[8] An estimation of Neurological Disability Index was also performed. 100% represented full disability or death, 81-99% represented profound disability (clinical stage-IV), 51-80% represented severe disability (clinical stage-III), 31-50% represented moderately severe disability (clinical stage-II), 1-30% represented mild disability (clinical stage-I) and 0% meant no disability.[9]

The rate of progression of clinical course was designated as; acute fulminant progressive form, diagnosed as the patient develops at least 66% neurologic disability (as measured by the neurologic disability index) in the first 3 months or death within 6 months, without classical manifestation of different clinical stages of SSPE, acute progressive form, diagnosed as development of at least 66% neurologic disability within 3 months of the first neurologic symptoms, with defined clinical staging, severe degree of disability exceeding 90% or death within 6 months; subacute progressive form diagnosed as having at least 66% neurologic disability within 9 months with defined clinical staging; and chronic progressive form, diagnosed as developing no defined clinical staging or evidence neurological disability as great as 66% until after 9 months from the first appearance of symptoms.[10] The study was approved by Ethical Committee of the Children's Hospital and Institute of Child Health, Lahore. Data was collected on a specially designed proforma. Descriptive analysis was performed for epidemiological variables like age, gender, nutritional and immunization status using statistic package for social science (SPSS) V.14. Frequencies of patients were calculated in age groups for age at time of immunization and/or contracting measles. Frequency of various clinical stages, SSPE stages and course of disease were calculated. Various factors were tested for significantly affecting the course of disease using Chi-square test. Pearson correlation (r) was used to determine any significant correlation between clinical course and epidemiological factor like age at the time of immunization and age at the time of contracting measles infection; $p < 0.05$ was considered as significant.

RESULTS

A total of 57 cases meeting the inclusion criteria were included in the study. Forty one of those patients were male and 16 female (M:F; 2.5:1). The mean age at presentation was 7.45 years, males presenting little earlier than females (mean age males 7.17 years, C.I 6.25-8.1 years, females 8.16 years, 95% C.I 6.4-9.9 years, p=0.45). Twenty five patients were underweight, mostly having 1st degree malnutrition (n=23, 40.4%). Majority of patients with manifested SSPE presented between 5-10 years of age. Forty patients (71.4%) were vaccinated for measles at about 9 months of age while 17 (29.8%) were unvaccinated. Thirty four patients reported to have measles in the past, 10 patients (17.5%) prior to their first birthday, 13 (22.8%) between 1-2 years of life and 11 patients (19.3%) after second year of life. Twenty three patients (40.4%) had no history suggestive of measles infection. Of the 34 patients with history of measles, 9 (26.5%) had symptoms of SSPE within first 3 years of measles eruption, 13 (38.2%) between 3-5 years, 9 (26.5%) between 5-10 years, while 3 (8.8%) after than 10 years. Only one patient (1.8%) had history of SSPE in the family. Most of patients had clinical stage-II (n=42, 73.7%) disease (Table I). Using the Neurology Disability Index, 6 patients (10.5%) had fulminant progressive course, 10 (17.5%) had acute progressive course, 29 (49.2%) had subacute course and 13 (22.8%) had chronic course.

Unvaccinated patients had more fulminant course than immunized patients (p = 0.04) (Figure 1). Among the

Table I: Clinical manifestation of SSPE in 57 patients.

Age of manifestation of SSPE (n=57)		
Age of manifestation	Frequency	Percent
Below 3 years	4	7.0
3-5 years	19	33.3
5-10 years	29	50.9
After 10 years	5	8.8
Total	57	100.0
Stages of SSPE at presentation		
Clinical stage		
Stage -I	3	5.3
Stage -II	42	73.7
Stage -III	10	17.5
Stage -IV	2	3.5
Total	57	100.0
Onset of SSPE after measles infection (years)		
Interval between measles and onset of SSPE		
Valid less than 3 years	9	26.5
3-5 years	13	38.2
5-10 years	9	26.5
More than 10 years	3	8.8
Total	34	100.0

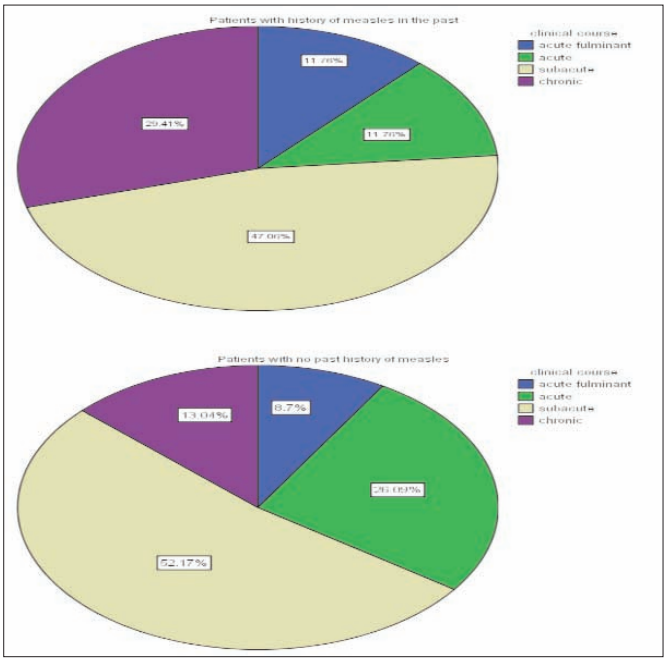

Figure 1: Course of SSPE in patients with and without history of measles.

patients with no history of measles in the past, males showed significantly higher incidence of subacute course of the disease than in females (64.7% vs. 16.7%, p=0.01). None of the other factors studied had any predictive value in determining the course of illness. There was no significant difference in the course of the disease between male and female patients (p=0.31). Malnutrition had no effect on the clinical course, (p=0.78). Age at contracting measles infection also had no significant correlation with the clinical course (r= 0.22, p=0.10). Age of onset of clinical manifestations of SSPE also did not predict the nature of expected clinical course (r= -0.03, p=0.81). Age at presentation also had no significant correlation with the clinical course (r= 0.11, p=0.41). Shorter duration between the age of contracting measles infection and onset of SSPE symptoms did had a trend of having more rapid course but correlated poorly (r= -0.02, p=0.91).

DISCUSSION

SSPE is a slowly progressive fatal inflammatory disease of central nervous system, developing as a sequel to childhood measles infection. The much higher preponderance of male patients (12:1) has been reported in earlier reports from India in mid seventies. However, recent works reported male: female ratio of 3:1 which is comparable to our results.[11,12] The cause remains illusive. Dyken *et al.* suggested that this observation may be related to hormonal influence.[2] Other experts believe that social circumstances are related to this disparity.

The average age of presentation worldwide is between 5 and 15 years with the mean age being 9-10 years.[1,2,13] The mean age of patients in this study was younger (7.45 years), though majority presented in 5-10 years age group. A recent study from the USA also reported mean age of onset of 7.9 years, in agreement with this study suggesting a gradual change in demographic characteristics of the condition.[4]

In this study, 71% of the patients were vaccinated for measles at about 9 months of age. It may be due to poor nutritional status of children, poor maintenance of cold chain, or due to a different type of strain in the environment. In another series of 48 patients, 7 cases (14%) of SSPE in previously immunized patients have been reported.[14] In immunized children, subclinical measles infection prior to vaccination has been postulated.[15] Epidemiological and virological data suggest that measles vaccination does not cause SSPE.[16]

Majority of patients had measles in the past (34/57, 59.6%), mostly at age less than 2 years. This may suggest that immune immaturity may play an important role in the pathogenesis of the disease.[10] Miller *et al.* documented history of measles among 74% of their 47 SSPE patients (median age 1.3 years).[17] The latent period between measles infection and SSPE is around 6-8 years in most of the cases, but wide range between 3 months to 23 years has been reported.[14,17] In this series, among the 34 patients with history of measles, most of the patients (64.7%, n=21/34) had a much shorter latent period (≤ 5 years after measles) similar to the findings from India.[18,19]

The pattern of clinical presentation has been noticed to change to an extent over the years.[7] In this study, most of the patients followed a subacute course (49.2%). This typical form includes the form identified by Jabbour.[8] This form follows the lines of classical SSPE and usually represents about 75% of all the patients. Chronic form of SSPE was documented among 22.8% patients. This is called atypical form. These atypical patients would present about 16-23% in various series.[12,20] Acute progressive form was documented among 17.5% using the Neurological Disability Index. The frequency of acute progressive form was still extra lesser than the classical form but much higher than previously reported figures (7-9%) from USA and India.[21] The shift of the disease following acute progressive course more than the classical subacute course was an interesting observation. The cause may be associated with poor nutritional status, newer measles virus strains or genetic predisposition. Further studies are required to determine the causative agents responsible for this change. Only 6 (10.5%) had a fulminant course. In the series by Risk and Haddad, approximately 10% of patients had fulminant progressive form.[9] Similarly Bojinova *et al.* in a 25-year epidemiology study, also found 4 patients (10%) with a fulminant course.[22] A fulminant course is seen at an older age of onset of symptoms and is associated with poor prognosis. In rapidly evolving SSPE, various stages of diseases

cannot be recognized. The exact mechanism producing an acute fulminant course is not known yet. Several factors such as exposure measles at an earlier age, viral virulence, impaired host defense mechanisms, and concurrent infections with other viruses have been suggested as responsible for producing rapid course of disease.[9,23,24] Unimmunized status was found to be significantly associated with a more rapid progress of disease in this study. This may again point towards the immune response of individual to initial measles exposure. None of the other factors studied in this study had any causative correlation.

Prognosis remains guarded in SSPE. The rate of progression is though variable, death occurs within 1-3 years after onset of symptoms.[4] In a study from USA about 10% of SSPE patients survived for 4-10 years with extended period of stabilization.[2] No spontaneous recovery was observed among any of SSPE patients. Nunes *et al.* documented spontaneous recovery in 5% of the SSPE patients.[14] This finding was not confirmed consistently by other workers.

CONCLUSION

Clinical course of SSPE cannot be predicted at the onset of this catastrophic disorder. Measles infection at younger age is the most important risk factor for SSPE. Children not immunized against measles had a significant rapid course of disease.

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