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# SUBACUTE SCLEROSING PANENCEPHALITIS

## CLINICAL ASPECTS AND PROGNOSIS

## THE BRAZILIAN REGISTRY

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ABSTRACT - Subacute sclerosing panencephalitis (SSPE) is an inflammatory neurodegenerative disease related to the persistence of measles virus. Although its frequency is declining because of measles eradication, we still have some cases being diagnosed. With the aim to describe epidemiological aspects of SSPE in Brazil, we sent a protocol to Child Neurologists around the country, 48 patients were registered, 27 (56 %) were from the southeast region, 34 (71%) were male and 35 (73%) white, 27 (56%) had measles, 9 (19%) had measles and were also immunized, 7 (14%) received only immunization, 1 patient had a probable neonatal form. Mean time between first symptoms and diagnosis was 12 months (22 started with myoclonus or tonic-clonic seizures, 7 (14%) with behavioral disturbances); 36 patients (75%) had EEG with pseudoperiodic complexes. Follow up performed in 28 (58 %) patients showed: 12 died, 2 had complete remission and the others had variable neurological disability Our data shows endemic regions in the country, a high incidence of post-immunization SSPE and a delay between first symptom and diagnosis.

KEY WORDS: immunization, measles, seizures, subacute sclerosing panencephalitis

**Panencefalite esclerosante subaguda, aspectos clínicos e prognóstico: Registro Brasileiro**

RESUMO - A panencefalite esclerosante subaguda é doença neurodegenerativa inflamatória relacionada à persistência do vírus do sarampo no organismo. Sua incidência vem diminuindo significativamente com a erradicação do sarampo, mas eventualmente alguns casos ainda têm sido diagnosticados. Com o objetivo de descrever aspectos epidemiológicos da panencefalite no Brasil contactamos Neurologistas Infantis de todo país. Foram registrados 48 pacientes, 27% da região sudeste, 34 (70%) do sexo masculino, 35 (73%) brancos, 9 (19%) apresentaram sarampo e receberam imunização, 7 (14%) somente imunizados, um paciente apresentou provável forma neonatal. Intervalo médio entre primeiro sintoma e diagnóstico de 12 meses, 22 pacientes (45%) iniciaram o quadro com mioclonus ou convulsões tônico-clônicas, 7 (14%) com distúrbios comportamentais; 36 (75%) apresentaram EEG com complexos pseudoperiódicos. Seguimento de 28 pacientes (57%) demonstrou 12 óbitos, 2 remissões completas, demais com sequelas neurológicas. Nossos resultados evidenciam regiões endêmicas no país, alta incidência de casos pós-imunização e demora na confirmação do diagnóstico.

PALAVRAS-CHAVES: imunização, sarampo, convulsões, panencefalite esclerosante subaguda.

Subacute sclerosing panencephalitis (SSPE) is an inflammatory neurodegenerative disease related to the persistence of an aborted form of the wild measles virus. Clinical presentation of the disease is more fully documented at this time but the major etiological and pathological bases of SSPE remain only partially understood[1,2]. The speed of progression has been designated as acute (development of at least 66% neurologic disability within 3 months of the first neurologic symptoms,

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defined staging, severe degree of disability exceeding 90% or death within 6 months), subacute (at least 66% neurologic disability within 9 months with typical staging), or chronic (does not show typical staging, does not evidence neurologic disability as great as 66% until after 9 months from the first appearance of symptoms)[2]. Although its frequency is declining in all countries because of measles eradicadication, we still have endemic areas throughout the world, mainly in countries where effective measles vaccination programs have not been established[3]. The incidence of natural measles in Brazil is declining in the last years. In 1991 we had 335:100000 cases and in 1994, 4.67:100000 cases. The immunization program covered almost 98% of children[4]. In spite of this we still have some cases of SSPE being diagnosed[5]. It was pointed out by Dyken et al.[6,7] a changing character of SSPE in the United States. The most striking feature of change was the rapid decline in its incidence.

The aim of this study is to describe the epidemiological aspects of SSPE in Brazil in the last years including comparison with the figures in other countries.

## METHOD

A protocol was sent to Child Neurologists in Brazil, which covered most of the country. The questionnaire was based on the recommendation "Demographic Data of the World SSPE Registry" and asked information about patients who had the diagnosis of SSPE during the period of 1990 to 1996. In the states where there was no Child Neurologist we sent the protocol to at least one neurologist affiliated to Brazilian League for Epilepsy or Brazilian Academy of Neurology. The ones that did not answered in 30 days were contacted again by telephone, fax or e-mail.

The diagnosis of SSPE were based on the guidelines of the International SSPE Consortium[3] and consisted of two major criteria: typical or atypical course and elevated measles specific antibody titers and at least 1 minor criterion: classical EEG with periodic slow waves complexes (PSWC) or elevated cerebrospinal fluid (CSF) measles - specific IgG or characteristic brain biopsy.

The patients registered were divided in three groups as follows. Definite SSPE: typical history marked elevated measles antibody or PCR confirmation of measles antigen. Probable SSPE: typical history CSF analysis, brain histology and /or EEG changes. Possible SSPE: patients show many typical clinical and laboratory characteristics of SSPE but immunological confirmation have not been accomplished or certain characteristics are missing.

SSPE clinical course was divided in 4 stages and subdivisions A and B as follows. Stage IA, behavioral, cognitive and personality changes; IB, myoclonic spasms. Stage II A, further mental-behavior deterioration, myoclonic spasms generalized and frequent; II B, apraxias, agnosias and motor signs. Stage III A, visual difficulties, no independent ambulation, myoclonic spasms more frequent and with long duration, seizures; III B, no spontaneous speech, may be blind, bedridden, dysphagia, movement disorders may appear. Stage IV, no myoclonic spasms, low voltage EEG, neurovegetative state.

An estimation of neurological disability was also performed. 100% represents full disability or death, 80-99% represents profound disability (stage IV), 50-80% represents severe disability (stage III), 30-50% represents moderately severe disability (stage II), 1-30% represents mild disability (stage I) and 0% no disability.

## RESULTS

84% of the child neurologists responded the protocol (Table 1). 48 patients were registered, 25 (52 %) had a definite diagnosis, 17 (35%) had a probable diagnosis and 6 (12%) had a possible diagnosis.

There were 34 males and 14 female. 35 (73%) were white. One patient had the rare neonatal type of SSPE. The rest varied in age of onset from 33 months to 27 years of age. The onset mean age of the series was 10 years (116 ± 59 months). The sex of the affected related to age at the first symptom. Males showed an increased rate at lower ages (Table 2). All the regions of the country were covered by corresponding Pediatric Neurologists or Neurologists. In just one state (Roraima) we did not found any Neurologist.

The geographic distribution of cases is shown in Figure 1. The majority of cases came from the East Coast, Southeast region (56%) and Northeast (25%). The states of São Paulo (29%) and Rio de Janeiro (22%) had the highest individual incidence. The accepted diagnosis of each patient was

*Table 1. Geographical distribution of questionnaires sent and responses.*

| Regions/States | Sent | Response |
|---|---|---|
| South | | |
| Rio Grande do Sul (RS) | 6 | 4 |
| Santa Catarina (SC) | 1 | 1 |
| Paraná (PR) | 2 | 2 |
| Southeast | | |
| São Paulo (SP) | 12 | 12 |
| Rio de Janeiro (RJ) | 6 | 6 |
| Espírito Santo (ES) | 2 | 2 |
| Minas Gerais (MG) | 1 | 1 |
| Central | | |
| Distrito Federal (DF) | 1 | 1 |
| Goiânia (GO) | 1 | 1 |
| Tocantins (TO) | 1 | 1 |
| Mato Grosso Sul (MS) | 2 | 2 |
| Mato Grosso Norte (MT) | 1 | 1 |
| Northeast | | |
| Bahia (BA) | 3 | 1 |
| Sergipe (SE) | 3 | 2 |
| Alagoas (AL) | 1 | 1 |
| Pernambuco (PE) | 5 | 4 |
| Paraíba (PB) | 2 | 1 |
| Rio Grande do Norte (RN) | 2 | 1 |
| Ceará (CE) | 4 | 3 |
| Piauí (PI) | 1 | 1 |
| Maranhão (MA) | 2 | 1 |
| North | | |
| Pará (PA) | 3 | 3 |
| Amazonas (AM) | 3 | 2 |
| Amapá (AP) | 2 | 2 |
| Rondônia (RO) | 1 | 1 |
| Acre (AC) | 1 | 1 |
| Total | 69 | 58 (84%) |

performed at a University or private tertiary hospital. Location of the domicile at birth was available in 47 patients, in 43 we had the state and city. 22 patients were born in cities that are the capital of their states and 21 in non-capital cities, this shows a rate of 1:1. We do not have the information, from the patients from the small cities and towns, if they came from rural or farm areas.

Mean time between first symptoms and diagnosis varied from 1 day to 13 years (12± 24.5 months). We observed generally advanced stages at the diagnosis (Table 3). The first more frequent symptoms observed were myoclonus (11 patients), tonic-clonic seizures (11 patients), behavioral disturbances (7 patients), learning disabilities (6 patients) and gait disturbances (5 patients). EEGs were performed on 45 patients, 36 (75%) had at least one EEG with periodic slow waves complexes or the formerly called Radermecker complexes. 39 patients presented with the classical or subacute form of SSPE. 3 patients presented the acute form and died within 6 months after the first symptoms. We had also one atypical patient with what we considered to be a mild newborn form of SSPE who had a spontaneous remission. The mother developed SSPE during gestation and the newborn was symptomatic (hypotonic and hypoactive) first days of life. CSF showed elevated measles antibodies (complement fixation 1:40)[8].

History of a previous measles infection was present in 27 cases (56%), not present in 8 cases (16%), and not available in 13 cases (27%). Age of measles infectious varied from 3 months to 9 years (26.6 ± 27 months). 18 patients (37%) had measles below two years of age, 14 patients (30%) had measles after two years of age and in 16 patients this information was not available (33%).

Measles immunization was performed in 19 patients, 9 do not received immunization and in 20 patients (41%) this information was not available. 9 patients had measles infection and also received immunization. 7 patients received measles immunization and had no measles infection related.

28 patients (58%) were followed during a period that varied from 1 month to 9 years (23 ± 27.5months). 12 patients died and 2 had complete remission of symptoms, one of them used isoprinosine for 12 months.

Neurological disability index of 100% was presented in 12 patients, 80-99% in 3, 50-80% in 8, 30-50% in 1, 1-30% in 2 and 0% in 2 patients.

*Table 2. Age of first symptom and male-female rate.**

| Age | Male | Female | Rate |
|---|---|---|---|
| > 4 Years | 4 | 1 | 4.0 |
| 5 - 9 Years | 11 | 6 | 1.9 |
| 10 - 14 Years | 14 | 5 | 2.8 |
| > 15 Years | 2 | 2 | 1.0 |

*In 3 patients age of first symptom was not available.

*Table 3. Stage of the disease at the diagnosis.*

| Stage | n | % |
|---|---|---|
| I A | 3 | 6% |
| I B | 2 | 4% |
| II A | 7 | 14% |
| II B | 11 | 23% |
| III A | 19 | 39% |
| III B | 5 | 10% |
| IV | 0 | 0% |
| Unknown | 1 | 2% |

## DISCUSSION

More males were affected than females as has been related in prior studies of this disease, and we do not have an explanation to this finding[7,9].

The only Brazilian state not covered in this report is a north state, which is extensively underpopulated. Here there are very few medical doctors, which might explain non-reporting.

We found that cases tended to cluster geographically, on the East Coast. In Brazil, the southeast region, which is a very populated region, has the highest incidence of SSPE. This finding is in agreement with this region having also a higher incidence of measles[4].

The cases registered where distributed with equal prevalence in rural and urban areas. We do not find a prevalence of rural areas as cited in previous studies[9,10].

As SSPE is a rare disease and the clinical diagnosis can be mistaken for other neurodegenerative diseases we found a delay between first neurological symptoms and definitive diagnosis. Sometimes this delay was within years. This also explains why over 50% of the patients had a diagnosis in later stages of the disease. A difficulty in confirming the diagnosis by immunological tests, sometimes because of the high costs of these methods was also a characteristic observed. The reasonably

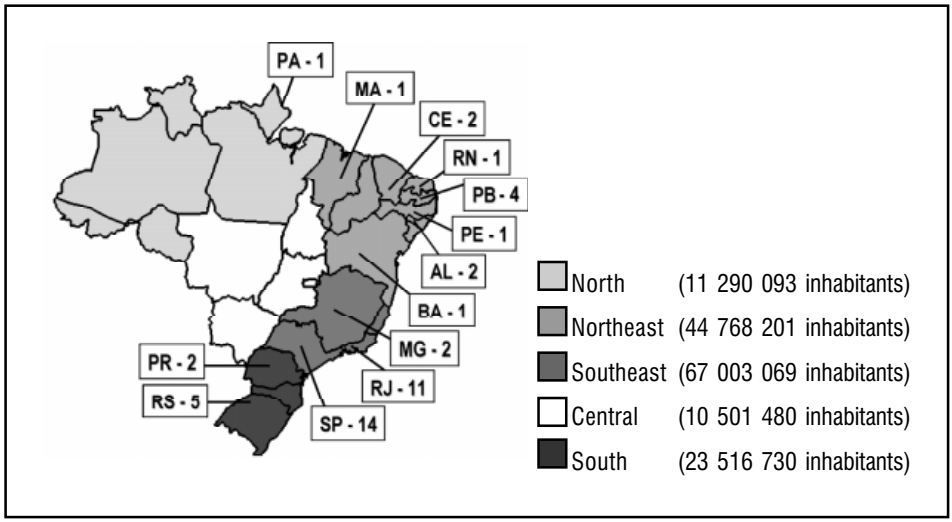


*Fig 1. Distribution of 47 cases per regions (North, Northeast, Southeast, Central and South).*

inexpensive EEGs when presenting with the characteristic periodic slow wave complexes were a very useful tool for the diagnosis.

The first symptoms related in the majority of cases were seizures or myoclonic spasms which brings more attention to the general physician than mild behavioral disturbances that can be seen on stage IA.

The incidence of measles in Brazil is decreasing every year and the immunization rate in the last six years has been increasing up to 90% levels. The number of cases of SSPE were also decreasing and this was the general impression from all the neurologists involved in this project.

Our incidence of post-immunization SSPE was around 14% and it was quite similar to that found by Dyken et al in their 1989 study. In Japan the incidence of measles vaccine-associated cases was lower, 5.4%. The type of vaccine used in Brazil is attenuated live virus, which is the same used in many other countries. What happens here is that besides the regular immunization scheme we repeat the immunization in One-day National Campaigns and some children for sure receive more doses than the regular schedule (9 and 18 months). We do not have accurate information on how many doses of immunization these children reported received.

Mean age of measles infection was not as low in the majority of patients as related in previous studies[9,11].

We had a high rate of mortality in the follow up, and also high indexes of neurological disabilities. This can be partly explained by the delay on the diagnosis, as it seems in some clinical trials that if the treatment can be effective, it is only in early stages[12,13]. We had two cases of spontaneous remission, the first one was followed for 9 years and had an absolutely normal neuropsychological development, he was treated with isoprinosine for 12 months and valproate. The second case was the patient with the probable newborn form, he was followed until 4 years of age with normal neuropsychological development and without seizures or myoclonus. We speculated if the disease in the newborn could be caused by a delay in the process of myelination with predominantly subcortical symptoms (hypoactivity and hypotonia)[8]. Anyway it has been also demonstrated that a newborn from a mother with SSPE during pregnancy can have transitory positive, perhaps maternal, measles antibodies[14].

Although SSPE is a rare disease we should be alert to the diagnosis, even if immunological confirmation is not readily available, the clinical course and EEG can also help in the diagnosis. Continued recognition is needed for proper diagnosis and treatment and this alert should reach the endemic areas.

Although a possible relation between measles vaccines and SSPE can be suggested, it is well known that the only way to eradicate SSPE seems to be by eradicating measles.

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