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EDITORIAL

Clinical expressivity in resurging SSPE: changing age of onset and new early symptoms

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Subacute sclerosing panencephalitis (SSPE) is still an interesting and provocatively mysterious disease in spite of the fact that the etiology, pathogenesis and clinical presentation are considered to be well worked-out and accepted by most pediatric neurologists and other scientists in the field. At present, many pediatric neurologists, in the USA particularly, consider the disease to be a disappearing entity. Most of my confederates in the USA consider the clinical aspects of the disease to be stereotypical. Yet it is because of this complacency, especially in the USA, that the article by Khadilkar et al. (1) in this issue of the Journal of Pediatric Neurology is a very important one.

There are two important concepts presented in this fine clinical and epidemiological study. First, it is shown that neither measles, the ultimate cause, or SSPE, the disease in question, have disappeared or are even disappearing in India specifically and in the world generally. Although India like many other countries in the world are considered "developing", data from the USA, supposedly a "developed" country would indicate that SSPE or measles for that matter have not disappeared, in fact, it is probable that a "resurgent" phase of prevalence is now present (1,2). Secondly, the authors present data which indicate, as others have previously (1-5), that SSPE is a disease which now appears to have altered epidemiological and clinical expression. Khadilkar et al. (1) show that their population of 32 patients have a much higher age of presentation and onset than was found in a previous study from the same region on 39 patients some 30 years before (6). Both studies showed a male predominance. Khadilkar et al. (1) found that in the early stages of the disease one fourth of their patients had the onset of visual loss which on later study with neuroimaging techniques was found to be due to demyelination in the occipital-parietal regions. This presentation was not seen in the previous study even though neuroimaging techniques were not developed in 1974. The authors carefully delineated other events in the early portions of the disease and related these and others to the history of vaccination which had only been done in nine of their patients. In the previous study no patients had been vaccinated. These new data may be both enlightening and confusing to the international pediatric neurological readership of this journal.

The authors do not clearly distinguish between "age of onset" and "age of presentation". Age of onset is historical and, considering SSPE, is especially dependent upon the retrospective report of concerned caretakers. This view may be considerably biased. Age of presentation or technically the age when the patient is first brought into the center who ultimately make the diagnosis is a figure which is related to semi-scientific assessment and is, therefore, a more concrete figure. The authors state that the age of presentation (which in SSPE Registry jargon is usually almost the same as "age of report", i.e. the age of the patient when the patient is reported to the registry, and "age of diagnosis", i.e. the age of the patient when the diagnosis has been established by the reporters) for their patients is 13.4 years. This mean age of presentation includes all 32 patients. They do not furnish us with figures for mean age of onset for the entire group but do state that in nine patients who received immunizations for measles the age of onset was 15.7 years. In the remaining 23 patients who had not been immunized, the investigators found a mean age of onset of 12.4 years. Combining these two groups allows a calculation of 13.3 years for the mean age of onset for the entire group. This would not agree with the figure that the authors give for the age of presentation since it would mean that only 0.1 years about 1 month separated their patients

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Table 1. Changing age of onset in different eras of immunization *

Countries	Pre-immunization	Developing	Developed immunization
USA	10.3 yrs	13.6 yrs	7.9 yrs
Turkey	9.8 yrs	13.0 yrs	7.6 yrs
India	11.2 yrs	13.4 yrs	-

* These figures are taken from the present one and the studies by Anlar et al. (5) and by Dyken (2-4).

from the very first symptom of their neurological disease to first clinic visit. Later in the paper they claim that the nine vaccinated patients averaged 3.2 months from first symptom to first clinic visit and the remaining non-immunized patients averaged 6.6 months, figures which would make the mean age of presentation to be 16.0 years and 13.0 years for the two groups and 13.8 for the entire 32 patients. Regardless, each of the figures (i.e. the authors' age of presentation of 13.4 years and mine of 13.8 years and my figure for age of onset of 13.3 years) are all much greater than what was recorded for the SSPE population from these Mumbaian centers in 1974. In 1974, the age of presentation was 11.2 years. I believe these differences, i.e. the difference between the 11.2 years taken from the "pre-immunization era" in India and the 13.4 years from the "developing immunization era" in India are strongly significant and are based on biological mechanisms (1).

In the pre-immunization era in the USA (those 362 SSPE patients reported before 1980) and in the developing immunization era in the USA (those 85 patients reported from 1980-1985), the mean age of onset was 10.3 years in the pre-immunization period and 13.6 years in the developing immunization period (Table 1, Reference 4). These are figures which match-up very well with the figures from India. Anlar et al. (5) did a wonderfully detailed study on patients from Turkey which is also comparable to these figures. These investigators found in a pre-immunization period (between 1975-1984 on 222 patients) that the mean age of onset was 9.8 years. In the developing immunization era (between 1990-1994 on 63 patients) the mean age of onset was 13.0 years. In addition, Anlar et al. (5) calculated the age of onset for yet another immunization era which I will call, the "developed" immunization era, that is in a period many years removed from the beginning of Turkey's national immunization program. In the period between 1995-1999 on 114 patients with SSPE, Anlar et al. (5) found the mean age of onset to be dramatically reduced to 7.6 years of age. Likewise, in a recent study from the USA sampling the 27 naturally born and raised patients with SSPE who were reported to the registry during this developed immunization era, the mean age of onset was 7.9 years very much in agreement with Anlar et al's study (Table 1).

Since all three of these epidemiological studies from quite different parts of the world are matched well, the figures as a group support the fact that the greatest variable in the statistical computation of this data is the immunological era rather than the geographic location. In regards to SSPE, both USA and Turkey should now be considered in a "developed" phase while India is still "developing". Such a distinction is important in analyzing the data presented in this fine article.

Several syndromes, types or forms of SSPE have been differentiated. One can delineate two groups of SSPE patients which can be called "typical" and "atypical". The typicals include the form identified by Dyken (4) as the subacute progressive form (SPF). This form follows the lines of classical SSPE but only represents about 75% of all the patients reported to the USA/World SSPE Registry. In fact, on a recent count of 61 patients reported in the USA, 47 were considered to have all the typical features of this syndrome. The SPF cases are very stereotypical. On the other hand, the atypical group of 14 patients are not stereotyped. Atypicals consist of what has been called the acute progressive form (APF), the chronic progressive form (CPF) and the two remitting forms one of which is chronic and one is subacute. At the last count of 61 patients, the CPF group represented 10 patients (16%), the APF group represented four patients (7%) and neither remitting form was represented. Khadilkar et al. (1) unfortunately did not classify their patients in this fashion and if they did it is unlikely that they would all have shown the same typical clinical type. The authors themselves claim that three of their nine patients who were vaccinated had a rapidly progressive course of illness. If the three patients had progressed to 66% disability within 6 months, they would have been classified as having the APF type of SSPE and would have represented 9% of their total patients. This figure would be comparable to the 7% which was alluded to in the recent USA study. Furthermore, if the six patients with unique presentations of SSPE (i.e. those six with first onset loss of vision) were all chronic atypicals this number would represent 19% of their population of patients. This figure would also be in agreement with the USA figures for the CPF type which was 16% (1).

It seems to this author that all demographic

data accumulated on SSPE patients should take into account differences in clinical presentation, particularly the type of SSPE identified. As an example, since 1989, 16 patients from India have been reported to the USA/World SSPE Registry. Fifteen of these or 94% were considered typical for SSPE with a course following subacute clinical dynamics. Yet one patient in this group was not typical. This patient at 3 years had the onset of intermittent epileptic seizures. Throughout early childhood while he continued to have intermittent seizures of a generalized tonic-clonic type, he was considered to be psychomotorly retarded which progressed in later childhood and school to what must be called a dementia. A few weeks before presentation at 11 years of age, he developed massive myoclonus and the diagnosis of SSPE was confirmed by strikingly elevated measles antibodies in the cerebrospinal fluid. It was interpreted that his age of onset was at 3 years, while his age of presentation was 11 years. He spent some 8 years demonstrating typical Stage I symptomatology. Since Stage I in classical SSPE lasts about 3 to 6 months, the slow course exhibited by this patient satisfied all the graphic criteria for the CPF type of SSPE as defined (4). One can see that his age of onset and age of presentation deviates greatly from the more set pattern shown by the other 15 patients reported from this country. One can also see that this patient's symptoms of neurological onset were not myoclonus, as it was for many of the typical patients, but epileptic seizures, which was followed by slowly progressive "psychomotor retardation". These cognitive and behavioral deficits, in fact, were stigmata of a slowly progressive neurodegenerative disease which characterizes the CPF type of SSPE. If the CPF patient was included in the calculations for the entire group, the age of onset would have been lowered from 12.5 to 11.9 years.

Although visual disturbance, seizures and behavioral changes are, in fact, characteristic for SSPE in its "early" stages regardless of the syndrome type, visual loss is not. Likewise, when a visual disturbance occurs, it is my experience that this seldom represents the dominant symptom as it was in Khadilkar et al's (1) series of six patients. In seven patients, these investigators were able to relate the visual loss to demyelination in the posterior cortical and subcortical areas. It should be pointed out that the demyelination detection had to be carried out at a later date than when the patients had the onset of their symptoms for it was probably from, at least, 3 to 6 months afterward when neuroimaging studies could have been done. We do not know the neurological disability of these patients when the neuroimaging studies were performed. Although the symptoms in six occurred obviously while the patient was in Stage I the neuroimaging studies could have been done when the patient had progressed already to Stage II. It has been my experience that frank demyelination occurs rarely in the early stages of SSPE. Lum et al. (7) in a neuroimaging study on seven SSPE patients separated these by their level of neurological disability. In three of the seven who were mildly disabled (that is those who were still in Stage I when they had their MRI scans with about 26%, 12% and 26% levels of disability) careful neuroimaging studies were normal or showed only questionable mild cerebral atrophy. These findings seem to be as expected since the pathological process in Stage I of SSPE usually reveals only the chronic inflammatory reactions seen in many of the viral encephalitities confined to the cortex and showing the intranuclear Cowdry body inclusions stigmatizing bags of altered measles virions. Certainly, it is not usually until Stage II that frank demyelination within the polio- and leukoencephalon would be expected. Yet, in Khadilkar et al's (1) six patients who had initial symptoms of visual loss and one other showed these abnormalities when they were later examined. In this series of 32 patients, one quarter demonstrated this unusual symptom early in the course of the disease in what is interpreted to be Stage I. Such is a remarkable finding, particularly since it was not seen in any of the 39 patients reported from their centers 30 years before.

It seems that the authors believe that all of their 32 patients were of the SPF type. Yet, at least three of their patients (all of whom were immunized) had a rapidly downhill course which would suggest that they were, in fact, examples of the APF type of atypical SSPE. In these patients, they reach a disability of greater than 66% within 3 months of onset and at least 90% disability by 9 months if they have not died before this time (4). Three such patients in a series of 32 represents about 9% of the population and this would be in agreement with the percentage of such patients in the much larger number of patients discovered in the postimmunized periods when reported to the USA/World SSPE Registry. If one assumes that six of Khadilkar et al's (1) patients with visual loss had the CPF type of SSPE rather than the classical form then these atypical patients would represent about 18% of the entire series. But why make this suggestion? Let us say that determining the symptom of onset is as difficult for the caretaker of any given patient as is the age of onset. When asked about the first symptom, the caretaker gives the more spectacular rather than the more subtle clinical feature. Subtle Stage I symptoms such as mildly progressive "psychomotor retardation" could conceivably be ignored. If all of the six patients had subtle Stage I symptoms for at least 9 months before the onset of visual loss they would fit the criteria shown by

Dyken to be typical of the profile of the CPF type of SSPE. If this were true the 18% would also be in agreement with the percentage of CPF patients seen in the USA reported patients. The presence of visual loss in six patients in the earlier stages of SSPE is still a highly significant new feature and would suggest that there is a changing expressivity in the way SSPE presents in Indian patients in a developing immunization era (1).

Comparison of several different populations of SSPE has shown that the institution of national immunization programs throughout the world has been associated in some fashion with changing the clinical expression of this disease. In the Khadilkar et al's (1) study, there was an increase in the mean age of onset, and a very important new observation of early symptoms which were not seen in similarly selected group some 30 years before. Whether the increase in age of onset/presentation was due to the presence of a syndrome which was not recognized by the 1974 group or not is not answerable by this author, but it is possible to speculate as to what caused it. Anlar et al. (5) and Dyken et al. (2-4) have suggested as have the authors themselves that 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 virion itself, changing its mode of operation with a new expression. Finally, this article is very important for it emphasizes that there is still much which needs to be known about this tragic disease, certainly both in the "developing" countries and in the so-called "developed" nations where it is still quite prevalent.

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