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Surveillance of Subacute Sclerosing Panencephalitis

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The disease we record as subacute sclerosing panencephalitis (SSPE) has four diagnostic criteria, the clinical picture, EEG pattern, serology, and histology.

The disease presents with an insidious onset of mental deterioration, perhaps first being noticed as a fall off in school performance or a change in behaviour. This is followed by motor dysfunction, often with myoclonic jerks and convulsions. Finally, there is a period of progressive decerebration with hypertonia, coma and ultimately death.

An abnormal EEG pattern is not present at all stages of the disease, but typically shows periodic bursts of high voltage slow wave complexes in all leads. They occur regularly at 3.5 to 20 second intervals and are often synchronous with the myoclonic jerks (Fig. 1).

Serology is essential for diagnosis. The cerebrospinal fluid contains a high level of measles antibody which correlates with bands of oligoclonal IgG. We consider that the most important diagnostic feature of SSPE is the low CSF to serum antibody ratio. Normally this is between 1 in 200 and 1 in 500 (Clarke *et al.*, 1965; Norrby *et al.*, 1974).

Inflammatory states of the central nervous system may sometimes result in an increased permeability of the blood-brain barrier (Sherwin *et al.*, 1963) but the picture in SSPE is very different from that seen in some other inflammatory conditions. Not only are there usually very high levels of measles antibody in the serum and CSF, but the CSF : serum ratio is low, even when the actual antibody levels are not exceedingly high. This is not simply indicative of a selective filtration of antibody, as may be seen by comparing the levels of poliomyelitis and measles antibody in patients with SSPE (Connolly, 1968a). The greatly decreased ratio of CSF : serum antibody in SSPE is evidence of local production of measles antibody within the central nervous system. This has been confirmed by other means (Tourtellotte *et al.*, 1968); for example, the increase in gammaglobulin in the CSF is greatly in excess of the levels of betaglobulin or albumin, and in the

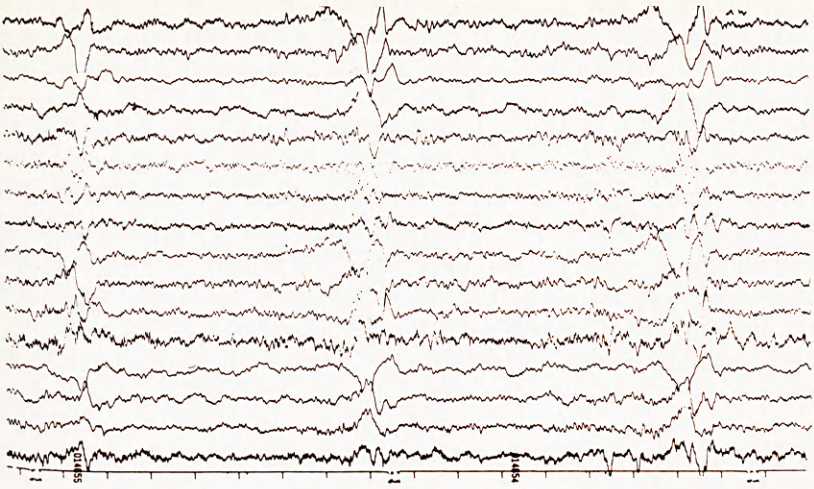

Fig. 1. EEG pattern typical of SSPE.

presence of the low CSF to serum gammaglobulin ratio the ratio of albumin in the CSF and serum is within the normal range.

Histology presents the least essential criterion. Inclusion bodies in cerebral cells can be demonstrated but it is not necessary to carry out a brain biopsy in order to make a diagnosis of SSPE.

AETIOLOGY

It has been shown that particles of antigen that stain specifically with fluorescein-labelled measles antibody (Connolly *et al.*, 1967) are distributed in cells in a manner that correlates with inclusion bodies (Lennette *et al.*, 1968). Electron microscope studies, too, have shown that the inclusion bodies consist of accumulations of smooth paramyxovirus-like nucleocapsids (Tellez-Nagel and Harter, 1966). However, there has been considerable discussion about the aetiology of what was called subacute inclusion body encephalitis of Dawson and subacute sclerosing leukoencephalitis of van Bogaert. It now seems that they were both describing the same disease, which is now called subacute sclerosing panencephalitis and is caused by measles virus.

In 1958, Pelc *et al.* claimed to have transmitted an acute central nervous system disease to monkeys from the brain of a patient with SSPE. Dick (1975) and Adels *et al.* (1968) were unable, in numerous attempts, to recover virus from SSPE patients from experimental hosts. Success was achieved only by co-cultivation techniques in which explant cultures from brain tissue of SSPE cases were grown in susceptible tissue cultures (Horta-Barbosa *et al.*, 1969, 1970). Some minor differences have been described between measles viruses recovered from

patients with SSPE and virus from uncomplicated measles, but it would be wrong to make too much of these minor differences in a virus that has undergone long residence in the central nervous system and has been subjected to various laboratory manipulations.

The clinical diagnosis may include Schilder's disease, and some cases of SSPE have probably been diagnosed as diffuse sclerosis, familial leukodystrophy or the syndrome that has been called adreno-leukodystrophy which occurs only in boys (Schaumburg *et al.*, 1972). The neuropathologists have had as much difficulty in sorting out this group as they have had with SSPE. If there is serological evidence of measles virus replication in the central nervous system, SSPE should not be given another name (Drysdale *et al.*, 1976) because of variances of the histopathology or because the disease may, like multiple sclerosis, run an acute course.

REGISTER OF CASES OF SUBACUTE SCLEROSING PANENCEPHALITIS

SSPE was first seen in Belfast (by G.D.) in 1965 when three fatal cases were observed. They were the only cases diagnosed between 1956 and 1965; in the ten years prior to that four fatal cases had been recorded, three of which had recurred in one year (Connolly, 1968b). The remarkable thing about these three cases was that they all had measles within six months of each other during an unexpectedly mild epidemic. This posed the question: would a mild virus like an avirulent vaccine virus be more likely to cause SSPE than a virulent wild virus? Because measles vaccine was being introduced at that time it seemed important to establish a base line of the number of cases of SSPE that were occurring in the UK. For this reason a national register was set up and has been maintained with the help of paediatricians, infectious disease specialists and neurologists who have notified cases and completed questionnaires. The register now contains data on 96 cases of SSPE reported between 1971 and September 1977.

Sex. There were 64 male and 32 female patients, giving a ratio of 2 : 1.

Age of Onset (Table 1). Age of onset was known in 93 cases, the mean age at onset of the disease being 9.8 years with a range of 3 to 27 years.

Year of Onset (Table 2). There has been little difference in the number of cases presenting each year since interest in the disease was first developed and the register started in 1971. We expect that a considerable number of cases with onset in 1977 have yet to be reported due to the inevitable delay between onset of the vague symptoms of the disease and the diagnosis being made.

Age at Time of Measles Infection (Table 3). There was a positive history of measles in 75 cases, in 17 it was unknown, and in 4 cases measles was definitely denied by the parents. Forty-eight per cent of the cases were under two years of age when they had their measles infection.

Delay between Measles Infection and Onset of SSPE (Table 4). The mean delay

Table 1. Age of onset of SSPE

Age in years	3-5	6-8	9-11	12+	Unknown
No. of cases	12	21	38	22	3

Table 2. Year of onset of SSPE

Year	1962	'67	'68	'69	'70	'71	'72	'73	'74	'75	'76	to Oct '77
No.	1	3	1	2	6	11	13	12	15	14	14	9

Table 3. Age at time of measles infection.

Age in years	<1	1–	2–	3–	4–	⩾5	Unknown	Denied
No. of cases	16	20	11	4	12	12	17	4

Table 4. Delay between measles infection and onset of SSPE.

Delay in years	<2	2–	4–	6–	8–	10–	⩾12	Unknown
No. of cases	2	8	18	19	16	7	4	18

Table 5. Date of death known in 34 cases.

Interval from onset of SSPE to death (in years)	<0.5	0.5–	1–	1.5–	2–	2.5–	⩾3
No. of cases	11 32%	10 29%	4 12%	2 6%	1 3%	1 3%	5 15%

was 6.8 years, the range being 1.5 to 18 years. There were three vaccination-associated cases in whom the delay was 4.5, 4.1 and 0.5 years.

Survival Time (Table 5). Of the 34 cases in whom the date of death is known, 61 per cent died within one year of the onset of the disease and the mean length of survival was 1.2 years. These figures, however, may be biased by the fact that many of the 34 patients known to have died were notified in recent years and some of the earlier cases about whom we have no information at the moment may have survived for a longer time. While the picture that has been presented is the usual pattern, the disease may run a more acute course in apparently normal

children (Kipps, 1977), and in patients under treatment for leukaemia (Breitfeld *et al.*, 1973; Sluga *et al.*, 1975; Drysdale *et al.*, 1976). Two patients in the latter category have been reported to the register but have not been included in the data described.

Incidence. A number of the cases reported were infected overseas, but it seems that the annual incidence of indigenous cases is about 0.2 per million total population, or about one per million of the childhood population. Three of the patients notified had received measles vaccine and a history of measles was denied. Although SSPE may be associated with measles vaccine virus, there is as yet no evidence in the UK that vaccine presents a serious risk. In the larger number of cases surveyed in the USA it seems that SSPE follows measles at a rate of approximately five to ten cases for every million children developing measles and that live measles vaccine may be associated with SSPE at a rate of 0.5 to 1.1 cases per million doses of measles vaccine distributed (Modlin *et al.*, 1977). Thus the risk of SSPE following natural measles is about five to twenty times higher than that following measles vaccination. A controlled study carried out recently in the USA showed that children with SSPE were significantly more likely to have had measles than controls and that control children were more likely to have had measles vaccine than SSPE cases. So vaccine protects against SSPE by preventing measles with its attendant higher risk of SSPE.

EPIDEMIOLOGY

To try to find out more about SSPE, the World Health Organisation set up a small international study group, on which G.D. was the UK representative. The pattern of the disease in those countries where it has been studied appears to be similar to what has already been described. Certain variations in the geographical distribution of the disease in some countries have been suggested, but they are not necessarily related to the geographical location itself but to other factors. It has been suggested that there may be racial predispositions to SSPE; for instance, in Southern Africa, where it appears to be a disease of non-whites (McDonald *et al.*, 1974; Kipps *et al.*, 1978), in Israel where the rates in Arabs and Sephardic Jews are at least six times higher than among Ashkenazi Jews (Soffer *et al.*, 1976), and in the USA where, in contrast to South Africa, SSPE is four times more common in whites than in blacks. There is no evidence that genetic factors could account for the ethnic or racial differences observed, and in part they could be explained by differences in the rural-urban distribution of different races. In the USA, the disease is more common in rural areas, and the greatest incidence has been found among children from farming communities. Preliminary data from a case control study suggests that SSPE cases are exposed to birds such as household cage-birds, domestic fowl and pigeons to a greater extent than are matched controls (Jabbour *et al.*, 1977).

There is no obvious explanation as to why children who develop SSPE have

their measles infection very early in life. It has been suggested that family size may affect the risk by influencing the age of exposure (Dick, 1975) and this was found in data from Israel (Soffer *et al.*, 1976). The higher incidence in rural than urban areas has already been commented on; if measles infection at an early age was the only significant factor in the pathogenesis of SSPE this is the opposite of what would be expected, for the age-specific attack rate among small children in cities is generally higher than in the country.

The virus/host relationship has not been discussed. Why does the virus lie dormant in the central nervous system of some individuals and what re-activates it? Why the delay? The answers to these questions are vital to the understanding of SSPE and many other slow virus infections such as progressive multifocal leukoencephalopathy, Creutzfeld Jacob disease, and, maybe, multiple sclerosis. Whatever theory is put forward must be consistent with the epidemiological findings.

This article is based on a paper read by Dr Dick at the Paediatric Conference held in the Royal College of Physicians in October 1977.

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