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SUBACUTE SCLEROSING PANENCEPHALITIS IN IRAN. CLINICAL AND IMMUNOLIGICAL CHARACTERISATION

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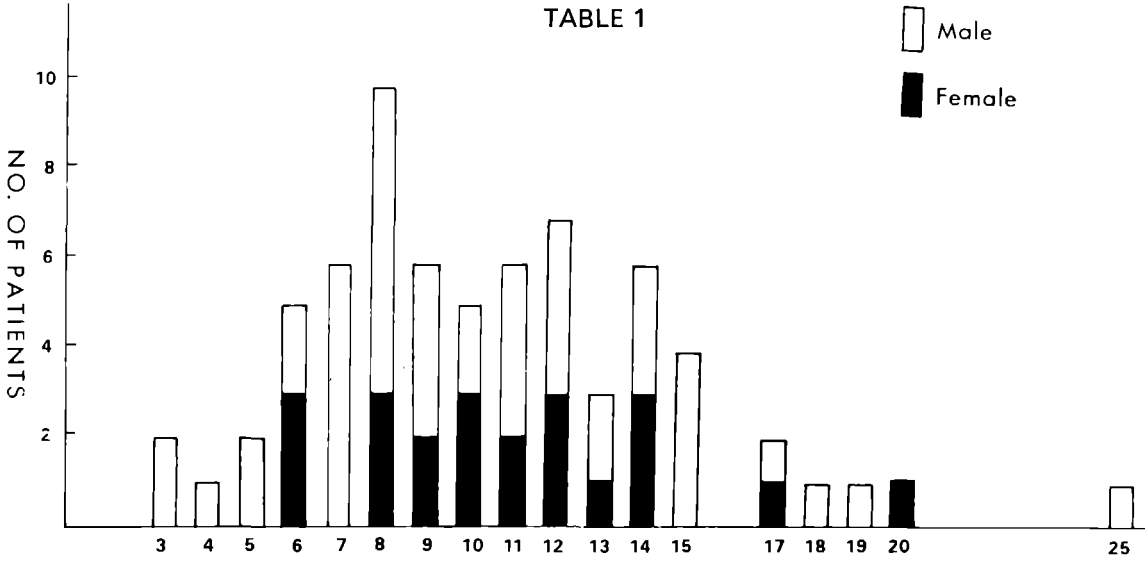
Subacute sclerosing panencephalitis (SSPE) is probably the commonest *known* viral infection of the central nervous system affecting children and young adults in Iran. The frequency of SSPE is given as one per million population in the course of a ten year period in the USA (Jabbour, 1971) and similarly in England (Leading Article, 1979). In Iran the condition is clearly far more common as with the total population of 35 million in the country, we have seen in one centre alone, (admittedly a referral centre) over 140 cases in the past 7 years and in our University Hospital, where most of these cases have been evaluated and investigated, we see an average of 1 to 2 new cases per month. In this report we present data on 110 of the above mentioned cases. The ratio of the male to female in our study is similar to the previous reports as about 70% of our patients were males.

The average age of our patients was 7.2 years with a range between 3 to 25 years (Table 1). Only two of our cases, a girl of 8 and a boy of 9 years had had measles vaccination previously. The age of measles infection was often not known but in 25 cases when this information was available measles infection had occured within the first two years of life in the majority of patients (Table 2). Our patients were almost entirely from rural areas, villages and from poor financial backgrounds and we have rarely seen cases from the so-called social class 1 or 2. Incidentally, this contrasts sharply with our experience of the social background of about 140 cases of multiple sclerosis investigated in Iran.

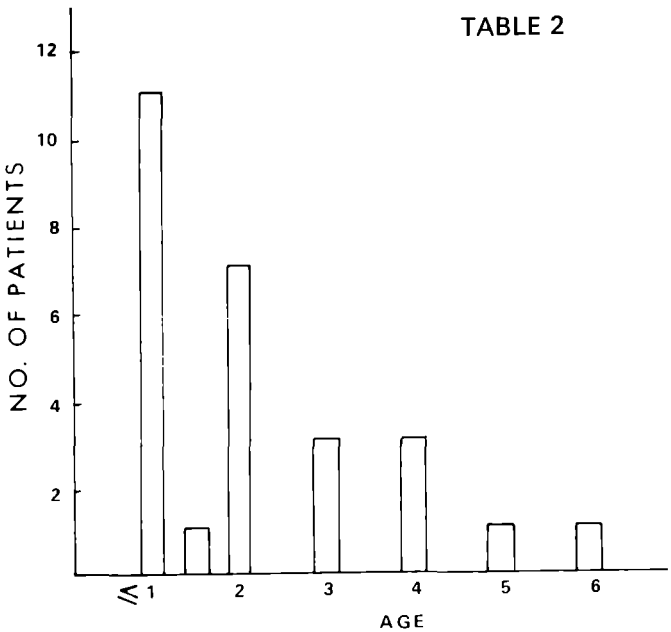
Proceedings of the first International Symposium on SSPE, edited by Fuad S. Haddad and Robert Matossian. Bouheiry Bros Press, Beirut 1983.

TABLE 1



Age & sex distribution of SSPE patients

TABLE 2



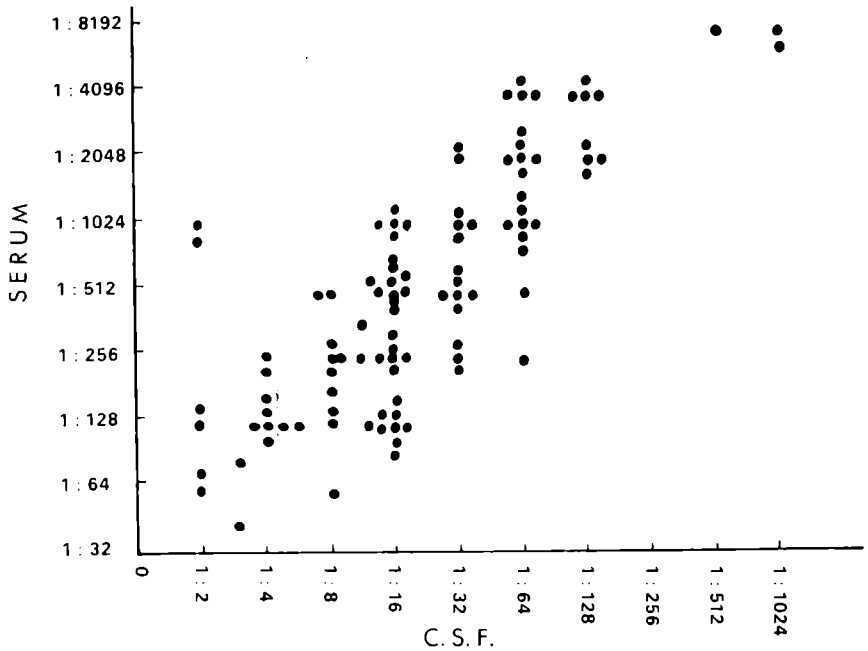
Age of measles infection

The diagnosis of SSPE in our cases was established by typical clinical features, electroencephalographic study, serological tests and tissue studies. There was an interval of from one month to five years between the onset of symptoms and the definite diagnosis. This was because of the poor travel facilities and the often long distances involved. Consequently some patients were seen in later stages of the disease corresponding to Jabbour's (1969) stage 2 or 3. The commonest form of presentation, as in Jabbour's series (1969), was mental changes, behaviour disturbances and poor school record etc. The changes mentioned were sometimes very gradual and occasionally patients were referred to and continued to be seen by psychiatrists for weeke to months before the condition was suspected often through EEG changes (Partovi). The second commonest presentation was myoclonic epilepsy. The myoclonous varied from very slighy, and detectable only with great care, to severe, causing sudden and recurrent falls. Generalised grand mal epilepsy was uncommon. Occasionally we saw cases for the first time, in late stages of total disability, unable to stand or walk, mute and with no sphincter control.

Measles haemagglutination inhibition (HI) antibody titres were routinely estimated in the blood and CSF. About 40 cases of other non related neuroligical disease were chosen and similarly tested. These 40 cases consisted of 10 patients with cerebral infarction, 10 with herniated intervertebral discs, 10 with Parkinson's disease and 5 each with motor neurone disease and myopathy. In only one of these 40 cases we had HI titre in the CSF to the dilution of 1:4, though the blood titres ranged from zero to 1:2048 (Table 3). It was concluded that a blood level above the figure 2000 and any appreciable level in the CSF in the absence of recent measles infection or inoculation was highly suggestive of SSPE. The highest blood level was of 1 in 16384 in a girl aged 5, only just recently seen, and the highest CSF level was 1 in 2000. The HI level in blood usually went up to diagnostic levels in 3 to 4 weels from the onset of the disease, although in 4 patients the CSF titre became significant later on in the course of the disease.

TABLE 3

Correlation of measles antibody in serum and C.S.F. in SSPE



The EEG was abnormal in almost all cases at sometime during the course of their illness. The typical changes were those of high voltage. slow activity and the highly suggestive burst-suppression pattern. In 10% of the cases the EEG was normal or near normal at the onset of the disease and in one case, a girl of 24, the EEG has remained normal for 30 months after the onset of her neurological disability. She had had gradual decline in intellect and corticospinal tract and severe cerebellar involvement (confirmed by biopsy). She had, however, positive serological findings and electron microscopic demonstration of measles nucleocapsid in her cerebellar biopsy material. Another unusual EEG was obtained from a 4 year old boy and consisted entirely of characteristic high voltage, slow complexes with a total absence (or suppression) of intervening cortical potentials.

Computed Scanning (CT) of the brain was done in almost all cases and did not show any specific diagnostic features in the early disease but often showed significant cerebral atrophy if and when repeated in advanced cases. Marked cerebral atrophy was found in a 16 year old boy with a five year history of progressive dementia, myoclonic jerks and rigidity. His EEG was not characteristic and final diagnosis was made on CSF and blood serological examination. In one case, a boy of 10, who had typical clinical and EEG findings of SSPE, the CT scan showed a large cystic posterior fossa lesion. On histological examination after the operation the tumour proved to be a cystic astrocytoma of the cerebellum. The anti-measles antibody titre of the xanthochromic fluid aspirated from the cyst was 1: 1024. Blood HI titre was 1:2048 and later 1: 9192, the CSF level 1: 128 and the saliva level 1: 24. The presence of this titre in the cyst fluid raises interesting hypotheses about the site of production of the antibody.

Twenty three cases were the subject of a full immunological study consisting of lymphocyte subpopulations ("active" T cells, total T cells, and B cells), leukocyte migration, lymphocyte transformation, complements (CH5O, C3, and C4), and immune complexes in serum and CSF. The results are reported elsewhere (Derakhshan *et al*, 1981). In that study we concluded that the percentage of T cells was normal. The number of patients with positive migration inhibitory response to phytohaemagglutinin was lower than controls, corresponding to the diminished percentage of total T cells in patients.

Of special interest was the demonstration of anti-measles antibody in the saliva of SSPE patients. The full results are reported elsewhere (Derakhshan *et al*, 1980). Two ml of saliva was obtained from 67 consecutive patients with SSPE at various stages of the disease (Table 4). The HI test was done on the saliva of patients and 25 normal control individuals. The HI test was negative in 19 patients (28.4%) and in all control subjects. Seven patients also had a submandibular gland biopsy. Another specimen was obtained from a patient who had a ventriculo-jugular shunt operation for a differnt neurological disorder which was used as a control for immunofluorescent staining (IF). All frozen section specimens of the gland from the patients showed IF staining, using fluorescent antihuman immunoglobulins. The control biopsy was negative. Measles HI titre in the sera of 14 individuals in the control group is variable, ranging from 1:16 to 1: 512 dilutions. No inclusion body or virus particles were seen on histological and electron microscopic examination of the biopsied material.

In eleven cases tissue diagnosis was possible with the brain biopsy and five cases had full post mortem examination. Immunofluorescence with anti-measles immune complexes was seen in all brain biopsies. In addition three cytopathic strains of SSPE virus were isolated from brain biopsies of three

patients. These strains were isolated and maintained by co-cultivation of infected brain cells with fresh Vero cells. The biological characteristics of two strains were studied. It was found that these strains remain cell-associated after repeated co-cultivation with Vero cells. The correlation with measles virus was demonstrated by the plaque reduction test and the immunofluorescence test. Intracerebral inoculation of monkeys, adult guinea pigs, newborn and adult hamsters or mice was followed by acute encephalitis and death. Full details are reported elsewhere (Mirshamsi *et al*, 1979).

TABLE 4

Total	Measles antibody titre (H I) in saliva								
	Neg.	Undil.	1:2	1:4	1:8	1:16	1:32	1:64	1:128
67	19 28.4%	4	10	8	9	7	7	2	1

Apart from the above cases we had a number of unusual features among our patients. (Derakhshan *et al*, 1974). Two patients were seen with a chronic progressive illness characterised by dementia, ataxia and spasticity. There were no myoclinic jerks and both had normal EEGs. Pathological findings in three brain biopsies were those of viral meningoencephalitis with perivenous demyelination. Serological data in both patients indicated the presence of measles virus infection. Intracytoplasmic structures resembling measles virus nucleocapsids were found in the brain biopsy of one patient and IF staining showed antibody in the temporal lobe biopsy of both patients. It was almost as if we had a link between SSPE and a demyelinating disease. Another interesting case was that of a 20 year old boy with a short history of mental change, epilepsy and speech disorder rapidly culminating in coma at the time of hospital admission. He had diagnostic HI titres in the CSF and blood. This was possibly a case of acute sclerosing panencephalitis. There was another case of an 8 year old boy with typical SSPE who at the age of two and a half years had developed nephrotic syndrome treated on twe occasions with steroids and Methroxate. While on these immunosuppressives he had developed measles. There were also five cases with chorioretinitis. The pathogenesis of this lesion has been established (Font *et al*, 1973; Robb *et al*, 1970). Two patients had marked papiloedema with venous engorgement but without exudates or haemorrhage. The papiloedema followed a benign course

in both patients with complete resolution while in hospital.

Further studies are in progress to create a proper SSPE Registry, the effect of measles vaccination on the frequency of the disease, and the efficacy of the various therapeutic agents.

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