Epidemiol. Infect. (1992), **108**, 547–553
Printed in Great Britain

Subacute sclerosing panencephalitis (SSPE) in Papua New Guinea: a high incidence in young children

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(*Accepted 9 December 1991*)

SUMMARY

Eighty-seven cases of subacute sclerosing panencephalitis (SSPE) were diagnosed from September 1988 to April 1991 in Papua New Guinea (PNG), by demonstration of high-titre measles-specific antibodies in cerebrospinal fluid (CSF). For 1990 the annual incidence of SSPE, for the study provinces, was calculated to be 56 cases per million under 20 years of age and it is expected that this figure will be higher in 1991. The mean age of presentation was 4·9 years, with a male to female ratio of 1·8:1. An elevation in the ratio of immunoglobulin G as a percentage of total protein in CSF and an increase in the CSF:serum immunoglobulin G ratio was shown in SSPE patients. The dramatic appearance and high frequency of the disease in PNG might relate to the early age of measles infection encountered in children in this country.

INTRODUCTION

Subacute sclerosing panencephalitis (SSPE) is a rare progressive disorder of the central nervous system caused by a slow measles virus infection. The disease is primarily one of children and young adolescents, the average age at diagnosis being 8–12 years. Prior to the extensive use of measles vaccine the annual incidence of SSPE in industrialized nations was reported to be 0·06–1 case per million [1, 2]. The majority of SSPE cases occur in those below 20 years of age, and if this group is used as the denominator instead of the whole population, the incidence has been calculated at 1–5 cases per million population under 20 years of age [1, 3].

The clinical presentation of SSPE is of variable and widespread disturbances of the central nervous system. It is not until overt demonstration of neurological problems emerge that the true nature of this illness becomes apparent and medical attention is sought. Most patients die within 2 years, but in a proportion

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of cases the course is much more rapid and death ensues after 3 or 4 months [2]. A study of 118 patients found substantial spontaneous improvement in only 5% of cases, while fewer than 7% were living more than 6 years after onset [4].

During the period September 1988 to July 1990, an annual incidence rate of 13 cases per million population under 20 years of age was confirmed in Papua New Guinea (PNG) [5]. With the exception of Australia and New Zealand this represented the first report of SSPE in any of the countries of the Western Pacific (Papua New Guinea, Solomon Islands, Vanuatu, New Caledonia, Fiji and Tonga). The current report expands our earlier findings.

SUBJECTS AND METHODS

A clinical diagnosis of SSPE was suspected in a previously well child presented to paediatric staff at one of the hospitals in this study with evidence of progressive deterioration of mental and physical ability, dementia and/or myoclonus. The disease was staged according to Jabbour and colleagues [6] and Dyken and colleagues [7]. The hospitals taking part in this study were Goroka Base Hospital, Eastern Highlands Province; Kundiawa Hospital, Simbu Province; Kudjip Hospital, Western Highlands Province; Madang Hospital, Madang Province; Popondetta Hospital, Oro Province; Tari Hospital, Southern Highlands Province.

Electroencephalography was not available at any of the centres. In most cases, cerebrospinal fluid (CSF) and blood were collected on the same day from each patient and sent to the Papua New Guinea Institute of Medical Research laboratory in Goroka. CSF samples visibly contaminated with blood were rejected and fresh specimens requested. The presence of measles virus antibody in CSF samples, pathognomonic for SSPE, was demonstrated by enzyme-linked immunosorbent assay (ELISA) [8, 9]. Samples from 80 SSPE patients, confirmed by ELISA, were further analysed serologically and biochemically; in seven of the confirmed cases insufficient volumes of CSF were available for further analysis. In 17 of the 87 confirmed cases, CSF alone was available; in an additional three cases inadequate volumes of serum were available. Samples from a group of 25 patients, who presented with some of the symptoms suggestive of SSPE but who were shown by ELISA of CSF samples not to be SSPE patients, were analysed in a similar manner. CSF total protein was measured by the method of Bradford [10] using the BioRad protein determination kit (BioRad Chemical Division, Richmond, Calif.). The concentration of total immunoglobulin G (IgG) in CSF and serum was measured by direct ELISA using a modification of the method of Musher and colleagues [11]. The total concentration of measles-virus specific IgG was determined by ELISA using the World Health Organization (WHO) International Standard for anti-measles serum. A pooled serum community standard was obtained from 25 healthy children less than 11 years of age, after natural infection or measles vaccination.

RESULTS

During the period September 1988 to April 1991, a clinical diagnosis of SSPE was suspected in 112 patients and confirmed in 87 by demonstration of high-titre measles virus antibody in their CSF. Three cases were diagnosed in 1988, 19 in

Table 1. *Biochemical and serological profiles in SSPE and non-SSPE patients*

	No.	CSF IgG (mg/dl) GM† (±1·96 S.D.)	CSF protein (mg/dl) GM (±1·96 S.D.)	IgG/TP %* Mean (S.D.)	No.	Serum IgG (mg/dl) GM (±1·96 S.D.)	CSF:serum IgG ratio ($\times 10^{-3}$) Mean (S.D.)
SSPE	80	14·8 (2·6–84)	59·0 (14·1–247)	28·3 (13·4)	67	2046·4 (904·1–4632)	9·9 (7·4)
Non-SSPE	25	1·3 (0·2–8·6)	35·6 (5·8–220)	4·3 (2·7)	18	2128·1 (767·4–5901)	0·9 (0·7)

* CSF total immunoglobulin G as a percentage of total protein (normal range 2·05–10·0 %) [14].

† Geometric mean.

1989, 47 in 1990 and 18 in the first 3 months of 1991. According to PNG 1990 census statistics, the total population for the provinces of origin of the SSPE cases was 1 682 652, with 50 % (841 326) of the population below 20 years of age [12]. Using this figure as the denominator, the annual incidence of SSPE in 1990 is calculated as 56 cases per million below 20 years of age. Goroka is the only centre in PNG able to assay measles-specific antibody and all suspect cases were referred there for diagnosis. However, no particular attempt was made to detect all cases occurring in the provinces in the study and it is highly likely that the calculated annual incidence rate for 1990 is an underestimate. If the trend shown during the first 3 months of 1991 is continued for the remainder of the year, the annual incidence rate for 1991 is likely to be significantly higher.

Collection of data in many areas of PNG is difficult, and clinical notes on many of the confirmed SSPE cases were not available. However, reliable information as to sex of the patient was available for 86 and age at presentation for all but 2 of the 87 confirmed cases. There were 55 males and 31 females; a male:female ratio of 1·8:1. Of these, 54 (62 %) were aged 5 years or less at time of presentation, and 11 (13 %) were less than 3 years of age. Mean age at presentation was 4·9 years with no significant difference between male and female patients.

Detailed clinical notes on history and clinical presentations were available for 48 patients, especially those presenting at Goroka Base Hospital. For this group of patients the reported length of symptoms before presentation varied between 4 and 16 weeks. Some had a history of measles at a very young age. Unfortunately, however, very little information regarding prior infections and measles vaccination history was available for the group as a whole.

The serological and biochemical profiles for SSPE patients and for the population of non-SSPE children is presented in Table 1. Adequate serum samples were available from 67 SSPE and 18 non-SSPE patients. In SSPE patients, the total IgG in CSF was increased in 62 of 80 patients (78 %), normal upper limit 8·4 mg/dl [13]; 6 of the 62 had a normal protein level of < 45 mg/dl [13]. Of 80 cases of SSPE, 75 (94 %) had an elevated ratio of IgG in the CSF, as a percentage of total protein (IgG/TP %). Of 67 SSPE patients 57 (85 %) had CSF:serum ratios of IgG greater than the mean normal ratio of $3{\cdot}3 \times 10^{-3}$ [13, 14].

Table 2 shows the estimates of measles-specific IgG titres in CSF and serum,

Table 2. *Measles antibodies in serum and CSF expressed in mIU/mg IgG*

	No.	Serum GM* (±1·96 S.D.)	No.	CSF GM (±1·96 S.D.)
SSPE	67	3342 (130·8–85365)	80	12972 (1460·0–115250)
Non-SSPE	18	1·2 (0·1–10·5)	21†	0·0
Pooled community standard‡		3·8		

* Geometric mean.

† Insufficient volumes of CSF were available in four non-SSPE samples.

‡ Pooled sera from 25 children after natural measles infection or vaccination (1230 mg/dl IgG).

expressed in milli-International Units per milligram total IgG (mIU/mg IgG). The SSPE samples showed a high titre of measles-specific IgG in both CSF and serum. The non-SSPE group and the pooled community standard serum had a significantly lower titre of measles antibodies than that found in SSPE patients.

DISCUSSION

In this study 87 cases of SSPE were identified on the basis of clinical features and the presence of high titres of measles virus-specific antibody in CSF. It is possible that some of these cases may have been post-measles encephalitis but the clinical presentation and the progressive nature of the symptoms suggests SSPE rather than encephalitis. The annual incidence of 56 cases per million below 20 years of age in the provinces studied is notably higher than previously reported from elsewhere. In the USA an incidence of 0·35 cases per million below 20 years of age has been recorded [15], while in Queensland, Australia the reported frequency from 1978 to 1983 was 1·21 cases per million of Queensland residents per year [2]. An epidemic in South India between 1983 and 1987 produced a calculated annual incidence rate of 4·3 cases per million under 20 [16]. The number of SSPE cases identified in the Indian study was thought to be as few as 10% of all cases occurring in that community [16], giving an estimated annual incidence of 43 cases per million under 20 years old.

A striking difference between the reported epidemics of SSPE in other parts of the world and PNG lies in the age distribution of the patients. In India the median age at diagnosis was 10 years, which is typical of SSPE [16]. In PNG the age at presentation is significantly lower, with a mean age of < 5 years.

The male : female ratio in our study was less than previously reported figures of 2·3 : 1 to 3·3 : 1 [1, 16, 17], although a recent report from Australia found no clear male predominance in the occurrence of SSPE [2]. A ratio of 1·8 : 1 agrees with the male predominance usually observed in SSPE; however, the male : female ratio of positives was the same as the presentation ratio of all suspect cases, and therefore may be confounded partly by the sex ratio of patients admitted to hospital.

In this study elevated CSF IgG levels were found in patients with SSPE, but the origin of this protein is not known. It is believed that the increase in IgG in the CSF seen in SSPE patients is due to local synthesis in the brain [18]. Serum IgG

levels in SSPE and non-SSPE children were similar ($P > 0{\cdot}5$) and in agreement with previously reported values for Papua New Guinea [19]. The increase in ratio of CSF : serum IgG in SSPE patients supports the notion of antibody formation in the CNS. When the immunoglobulin to total protein ratio in the CSF was considered the ratio observed in the SSPE children agrees with the characteristic pattern encountered with other CNS lesions [13].

Paediatricians in Papua New Guinea have confirmed that before 1987 very few patients presented with symptoms suggestive of SSPE. The recently observed high incidence of SSPE in PNG may relate directly to the changes in measles epidemiology which have occurred in the country. A study of paediatric admissions to Goroka Base Hospital found a tendency for more recent measles admissions to be younger than previously reported; 50% of all measles admissions were under 12 months of age during the 1980s [20]. According to statistics issued by the Department of Health, measles is a problem affecting most parts of the country [20]. It has been well documented that age at measles infection is an important parameter in the subsequent development of SSPE [21].

We know little about the mechanisms which lead to the establishment of a latent measles infection, although it is obvious that the immune system fails to clear the virus from the body, even in the presence of very high levels of virus-specific antibody in serum and CSF. Rittner and colleagues have shown a significant association between partial deficiency of complement component four (C4) and development of SSPE [22]. However, in a recent study, serum C4 concentration was found to be at least as high in highland Papua New Guinean children under 1 year of age as in an expatriate control group [19]. The normal rarity of SSPE may be explained by the measles virus escaping neutralization through a 'window', open only at a narrow range of antibody concentrations [22]. In the highlands of PNG, children lose maternal antibodies at a very young age compared to European and Northern American populations [9]. It is possible that the 'window' exists for a longer period in these children than in children in other environments.

With the implementation of measles vaccination programmes the incidence of SSPE in other countries has decreased. A detailed study of measles, measles vaccination and SSPE in Israel found that the incidence of SSPE dropped sharply 10 years after mass measles vaccination was introduced [23]. This delay corresponded to the median age of onset of SSPE, hence the suggestion of correlation between this decrease and routine vaccination. In PNG a measles immunization programme began in 1982, but with few exceptions measles coverage until recently has been disappointingly low. In 1989 the average percentage of vaccinated children rose to 52·4% [24]. With an increase in vaccination coverage a decline in the number of SSPE cases seen each year can be expected. However, since the patients currently presenting with SSPE have a mean age of less than 5 years, these may represent only a small fraction of the total number of latent infections currently established. It is possible, even in the absence of the establishment of new latent infections, that the number of SSPE cases will continue to increase, with a concomitant rise in the mean age at presentation. A decline in the number of SSPE cases seen each year in Papua New Guinea may therefore not occur for some time.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Dr P. Watt, of Madang Hospital, for clinical data and sample collection, and Don Lewis for assistance with statistical analysis. We wish also to thank Dr K. Nemba, of Kundiawa Hospital, and other paediatricians in Papua New Guinea hospitals for collection of samples.

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