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A continuing high incidence of subacute sclerosing panencephalitis (SSPE) in the Eastern Highlands of Papua New Guinea

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SUMMARY

The aims of this descriptive study were to confirm the high incidence of subacute sclerosing panencephalitis (SSPE) previously reported from Papua New Guinea (PNG) and to relate SSPE to previous measles vaccination and measles illness. From February 1997 to April 1999 we diagnosed a total of 55 patients with SSPE at Goroka Base General Hospital in Eastern Highlands Province (EHP) of PNG. The diagnosis was based on high cerebrospinal fluid and serum measles virus antibody titres with progressive neurological disorder and myoclonic jerks. Of these 55 patients 42 were from EHP, including 32 whose onset was in the 2-year period 1997–1998. The annual incidence of SSPE in EHP in these 2 years was 98 per million population under 20 years of age, the highest ever reported. This incidence was more than ten times higher than the highest incidence in the prevaccine era reported from elsewhere. The mean age of onset of SSPE was 7·7 years (range 2·8–14·8 years) and the interval between measles and the onset of SSPE, where known, had a mean of 5·9 years and a range of 2·5–11·1 years. Among the SSPE patients 19 had a documented history of measles vaccination. Eight of these 19 also had documentation of previous measles illness; of these, seven were vaccinated after the development of measles and one was vaccinated 20 days before measles illness. Two non-SSPE children received vaccination twice which was documented and subsequently developed measles which was also substantiated by documentation. Two patients with SSPE yielded amplified nucleotide sequences of measles virus that were different from any of the vaccine strains. We found no evidence to implicate measles vaccination in the development of SSPE.

INTRODUCTION

Subacute sclerosing panencephalitis (SSPE) is an invariably fatal disease of the central nervous system (CNS) that affects mainly children. The precise mechanism of its pathogenesis is not established yet, but accumulated evidence suggests that in SSPE measles virus (MV) particles are incompletely eliminated by the immune system [1–4] and persist in infected cells in the brain, spreading from cell to cell and eventually culminating in the development of the disease. Most of the MVs isolated from SSPE

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Table 1. *Selected reported high incidence rates of SSPE from various regions*

Place of study	Study period	Incidence rate		Age of the study child population (years)
		PmTppy*	PmCppy*	
Prevaccine era				
New Zealand [14]	1956–1966	2·6	6·6	0–19
Southern Africa [15]	1970–1974	3·0	5·9	0–19
Postvaccine era				
Karachi, Pakistan [16]	1974–1985	6·35†	11·6†	0–19
Romania [17]	1985–1987	6·95	22·85	0–19
South India [18]	1983–1987	21·4‡	43·1‡	0–19
Papua New Guinea (PNG) [19]	1990	28	56	0–19
Eastern Highlands Province PNG (this study)	1997–1998	50	98	0–19

* PmTppy, per million total population per year; PmCppy, per million child population per year.
† Indirectly estimated.
‡ Assuming that 10% of the cases had access to laboratory diagnosis.

patients are cell-associated and do not produce infective particles. These viruses are characterized by a defective expression of M protein arising from a highly mutated genome, especially involving the M gene [5]. The highly mutated MVs expand clonally throughout the brain from the original measles virus that had entered the brain cells [6]. Moreover, it has been observed in SSPE that the expression of the distally located genes F and H are suppressed [7]. The restriction of these proteins may assist MV in escaping detection from the host immune system and lead to the persistence of the virus in the brain [8]. Although infant T cells can be primed with MV antigen even in the presence of passive antibodies, the adaptive immune responses of infants are limited in comparison with those of adults [9]. This supports the idea that the naive immune system of infants may provide an ineffective barrier to viral dissemination in the brain [10] and may explain the age-dependent risk of SSPE [11].

The illness is rare, reported incidence per million population per year ranging from 0·1 to 6 [12, 13] though higher figures have been reported from at least five other countries [14–20] (Table 1). The highest recorded incidence, which was 56 per million population below 20 years of age for 1990, had been reported from Papua New Guinea (PNG) [19]. Our present study confirms this unusually high incidence in the Eastern Highlands Province of PNG and describes the status of measles immunization and illness among SSPE patients.

METHODS

Patients

From February 1997 to April 1999, paediatricians at Goroka Base General Hospital (GBGH), Eastern Highlands Province (EHP), enrolled into the study 80 patients, including 64 who presented with clinical features suggestive of SSPE. Blood and cerebrospinal fluid (CSF) specimens for the determination of measles antibody titres were collected from these 64 and 16 other patients, five with CNS disease and 11 with measles, who were recruited from inpatients and outpatients at GBGH during the study period to provide a comparative group for measles antibody titre. Subsequently two of the comparative group fulfilled the criteria for SSPE, and 11 of the presumptive SSPE group proved not to have SSPE, but all 80 patients were followed as the study population.

Diagnostic procedures

Quantitative serum and CSF MV-specific IgG antibody estimation was performed with an enzyme immunoassay (EIA) kit (Denka Seiken Co. Ltd, Tokyo, Japan). Before being assayed, sera were diluted 1 in 200 and CSF 1 in 20 with the buffer solution provided.

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EIA values of both diluted serum and CSF specimens were determined from estimated optical density (OD) using a standard curve drawn up by plotting OD against a series of dilutions of pooled antibody-containing sera. The EIA value of a diluted specimen thus determined refers to the maximum dilution at which the specimen gave a positive result for the presence of antibody. The EIA value of diluted specimens with a passive haemagglutination (PHA) titre of 32 (the minimum titre at which the specimen gave a positive result) was defined as 4, arbitrary units and EIA values $\geqslant 4$ were regarded as positive, between 4 and 2 as equivocal and <2 as negative for the presence of measles antibody. The dilution factors of sera and CSF were corrected for in the final results by multiplying EIA values of diluted serum specimens by 200 and diluted CSF specimens by 20.

An electroencephalogram (EEG) was recorded in 14 patients, six using a two-channel EEG machine at the beginning of the study and eight using a ten-channel machine in the later part of the study.

Reverse transcriptase-polymerase chain reaction (RT-PCR) was performed on CSF and peripheral blood mononuclear cell (PBMC) specimens of 19 patients using primers that amplify the hypervariable region of the N gene of MV. Details of the methods and these results have been reported elsewhere [21].

Diagnostic criteria

Patients were categorized into *SSPE*, *probable SSPE*, *probably not SSPE*, *definitely not SSPE* and *inconclusive*. The diagnosis of *SSPE* was based on the presence of the following criteria: (1) progressive neurological disorder, particularly mental or motor deterioration, associated with a history of or the presence of sudden jerky movements or falls, with or without observable myoclonus or atonia, at least in one stage of the disease; (2) CSF EIA values of >2000 together with serum EIA values of $>200\,000$; (3) periodic synchronous discharges (PSDs) in the EEG consisting of bilaterally and simultaneously occurring periodic high-voltage slow wave complexes with or without sharps and/or spikes, appearing every 4–10 s, recorded at least once in the course of the illness [22–24]; and (4) positive amplification of a nucleotide sequence of MV with RT-PCR. Criteria 1 and 2 were both essential for *SSPE*. Criterion 3 was not essential since typical EEG changes may not be observable in some early and late cases [23] and typical PSDs may be masked by atypical EEG changes [22]. Criterion 4 was not essential since the MV genome could not always be amplified by RT-PCR [21].

With respect to criterion 2, SSPE was ruled out and the case classified as *definitely not SSPE* when the CSF or serum EIA value was <40 or <400, respectively. When the CSF or serum EIA value was between 40 and 200 or between 400 and 20 000, respectively, the case was classified as *probably not SSPE*.

Patients were classified as *probable SSPE* when they fulfilled criterion 1 but not criterion 2 and had either a CSF or serum EIA value of >1000 or $>100\,000$, respectively. In cases where the clinical features and course of the disease were consistent with SSPE but the clinical records were incomplete, so that criterion 1 could not be formally satisfied, patients were classified as *probable SSPE* if their CSF EIA value was >1000 and the serum value was $>100\,000$. All cases fitting none of the four categories defined above were classified as *inconclusive*.

History of measles immunization and illness

History of measles immunization and past measles illness was taken from an accompanying parent, close relative or guardian and substantiated by the child health record book (CHRB) or other documented sources wherever possible.

Calculation of the incidence of SSPE

Average annual incidence of SSPE in EHP for the years 1997 and 1998 was calculated based on the year and place of clinical onset. A total of 55 SSPE cases were registered at GBGH during the 27-month study period from February 1997 to April 1999. Among them, 42 patients resided in EHP at the times of both the clinical onset of SSPE and the registration at GBGH as SSPE. Of the 42 who resided in EHP 32 had their onset between 1 January 1997 and 31 December 1998. The numerator for annual incidence was exactly half this number and the denominator was the average population under 20 years (or 15 years) of age in EHP for 1997 and 1998.

RESULTS

Diagnosis

Among the 80 patients who were enrolled into the study, 41 were diagnosed as having *SSPE* and 14 as

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Table 2. *Serological results expressed as logarithm of EIA value*

	Diagnosis			
	SSPE	*Probable SSPE*	Measles	CNS disease other than SSPE
$\log_{10}$(CSF EIA* value)				
(number of patients)	(40†)	(9‡)	(3)	(3)
minimum	4·02	3·28	<1·60§	<1·60§
median	4·52~4·54	4·53	<1·60§	1·87
maximum	5·12	4·89	1·95	1·91
mean	4·40	3·93	1·52	1·70
±S.D.	±0·26	±0·58	±0·37	±0·34
$\log_{10}$(Serum EIA¶ value)				
(number of patients)	(40†)	(13‡)	(10)	(3)
minimum	5·55	5·09	<2·60§	3·11
median	5·80~5·81	5·74	3·47~3·57	3·20
maximum	6·26	6·23	4·14	3·38
mean	5·84	5·24	3·31	3·23
±S.D.	±0·18	±0·38	±0·74	±0·14

* CSF EIA.

† Number of patients whose clinical specimens, CSF or serum, were available for serological study. In one *SSPE* patient the measles antibody estimation was performed with a different system from that employed in the other 54 SSPE patients so this patient was excluded in calculating mean and SD.

‡ Serum was unavailable in one *probable SSPE* and CSF unavailable in five *probable SSPE* cases.

§ We substituted 1·30 ($=\log_{10}20$) for <1·60 ($1{\cdot}60=\log_{10}40$) and 2·30 ($=\log_{10}200$) for <2·60 ($2{\cdot}60=\log_{10}400$) in calculating mean and SD.

¶ Serum EIA.

probable SSPE. The diagnosis of SSPE was ruled out in nine cases (*definitely not*), determined to be *probably not* in 11 and was *inconclusive* in five. Table 2 summarizes the serological results. Typical PSDs were recorded in four cases of *SSPE*.

The hypervariable region of the N gene of MV was amplified from the PBMC specimens of two *SSPE* patients, but not from the CSF, and not from the PBMC specimens of 11 acute measles patients. Both nucleotide sequence and phylogenetic tree analyses showed that the amplified MV cDNAs were closely related to one another and belonged to the D3 genotype though they differed from any previously reported MV sequences. No genome sequences of vaccine strains were detected. The two SSPE patients who gave positive PCR amplification of the MV genome had been vaccinated twice and also had measles. Details of these results have been described elsewhere [21].

For further analysis and discussion, the 41 cases with *SSPE* and the 14 with *probable SSPE* were combined and referred to simply as SSPE.

Clinical features

The 55 SSPE patients comprised 31 males and 24 females. There were no important age differences by gender. Among the 55 patients, case protocols were preserved in 52 and misplaced in the other three. Of the 52 with preserved case protocols 42 came from EHP, seven from Simbu Province, two from Western Highlands Province and one from Madang Province. Of the 52 patients 50 had jerks and/or falls and in the remaining two they were undetermined (that is, there were only five patients in all with probable SSPE who did not fully satisfy criterion 1).

Of the 22 patients with known age at measles vaccination, two received it between four and five months, six between six and eight months, seven between nine and 11 months, and the other seven at 12 months (mean 19±29 months, median 10 months). Of the 18 patients with known age at measles illness, four had it between two and five months, eight between seven and ten months, two between 14 and

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18 months, three between 29 and 46 months, and the other one at 75 months (mean 17±19 months, median 9 months).

The age at onset of SSPE was known in 50 patients, in whom it was between 2·8 and 14·8 years (mean 7·7±2·9, median 6·9–7·0). The interval between measles vaccination and the onset of SSPE was known in 20 patients, in whom it was between 2·7 and 14·3 years (mean 7·0±2·9, median 6·0). The interval between measles and the onset of SSPE was known in 18 patients, in whom it was between 2·5 and 11·1 years (mean 5·9±2·1, median 5·5–5·7).

Further clinical features of the 55 and an additional 28 SSPE patients are described elsewhere, with the four patients' EEG records containing typical PSDs [25].

Combined documented histories of measles immunization and past measles illness

Of the 55 SSPE patients, 33 were vaccinated (in 19 of whom the history of measles vaccination was substantiated by the CHRB) and four were unvaccinated. In the other 18 the history of measles vaccination was uncertain or not studied. Among the 19 children whose history of measles vaccination was substantiated by the CHRB, 11 gave a history of receiving measles vaccine twice and two were vaccinated three times, all these vaccinations being substantiated by the CHRB. Of the 55, 20 had measles (in eight of whom the history of measles was substantiated by the CHRB) and 19 had no record of measles. In the other 16 the history of measles was uncertain or not studied.

Combined histories of measles vaccination and measles of the 17 patients whose histories (positive and negative) of both measles vaccination and measles were substantiated by the CHRB divided the patients into eight who were vaccinated and also had measles, seven who were vaccinated and had no measles, and two who were unvaccinated and had no measles. Among the eight who were vaccinated and also had measles one was vaccinated 20 days before having measles and seven were vaccinated after measles infection, with intervals between the illness and the first vaccination of 7 days, 13 days, 15 days, within 27 days, seven weeks, 13 months and 4 years. Among the non-SSPE patients two had been vaccinated twice (both documented) and subsequently developed measles which was also substantiated by documentation.

Population data

According to the 1990 national population census, the projected population under the age of 20 years (or 15 years) in EHP for the years of 1997, 1998 and 1999 was 162 052, 163 429 and 164 818 (or 132 855, 133 983 and 135 113), respectively. To calculate these figures the ratio below 20 years (or 15 years) in EHP between 1997 and 1999 was assumed to be the same as that in 1990, i.e. 50·8% (or 41·7%) [26].

Incidence of SSPE in EHP

Based on the number of cases with clinical onset of SSPE in EHP during the two years 1997 and 1998 (from January 1997 to December 1998), we have estimated the annual incidence rate of SSPE in EHP for the two years. That was 98 cases per million population under 20 years of age (or 120 cases per million population under 15 years of age). In this calculation the numerator was the annual number of cases who resided in EHP when their SSPE was manifested, which was 32÷2=16, and the denominator was the average population under 20 years (or under 15 years) of age in EHP for 1997 and 1998, which was 162 741 (or 133 419). This incidence was more than ten times higher than the highest incidence in the prevaccine era reported from elsewhere (Table 1).

DISCUSSION

There were 41 *SSPE* and 14 *probable SSPE* cases in the current series, making 55 cases in all. EHP is one of the five highland provinces that constitute part of the central mountain range of PNG. The province comprises six districts, each consisting of three to nine census divisions of around 30–100 villages each. There are geographical, economic and social barriers in many parts of EHP that hinder free transportation of patients to and from GBGH, which is the only referral hospital in the province. Therefore, the incidence of SSPE in the period covered by our study is very likely to be an underestimation. Nevertheless, the average annual incidence rate in this study is still more than 16 times higher than most of those reported from other areas [12, 13] and more than twice that of the highest reported incidence rate outside PNG (Table 1). Since the completion of this study we have registered 28 other cases of SSPE during the 20 months from April 1999 to November 2000 indicating

that the high incidence continued into the second half of 2000.

The characteristic EEG finding of typical PSDs strongly supports the diagnosis of SSPE if associated with serological evidence [22–24]. Unfortunately, access to EEG facilities is usually lacking in most developing country settings. For instance, 10-channel EEG facilities were not available at GBGH until the later part of the study. To diagnose SSPE reliably in the absence of EEG facilities we therefore decided to include a positive history or the presence of sudden jerky movements or falls, with or without observable myoclonus or atonia, within the primary diagnostic criterion. The reason behind this is that myoclonus (leading to jerky movements) or atonia (leading to falls) is time-locked to EEG periodic complexes and neither occurs independently from PSDs [24]. By this classification some early SSPE cases may be missed since in the early stages of SSPE myoclonus or atonia may not be clinically evident and may be detectable only with video-split EEG [24].

Highly sensitive RT-PCR methods have been used to detect the MV genome from throat swabs, CSF, blood and other clinical specimens in MV-specific IgM-positive cases of clinically suspected measles [27]. However, only a very few cases of successful detection of the MV genome have been reported in SSPE with these RT-PCR methods [28, 29]. In a concurrent study, we have been able to demonstrate MV genome in a small proportion (2/19) of PBMCs and none in the CSF specimens from SSPE patients despite a high success rate (11/14) with throat swabs from acute measles cases [21]. Therefore with the current RT-PCR methods a positive result supports the diagnosis of SSPE but a negative result does not exclude it.

Among the SSPE patients with available documented information in this study 19 had received at least one dose of measles vaccine. Clearly, the vaccines used were ineffective in preventing measles and/or SSPE. It is of interest to note that among the eight SSPE patients who had documented positive histories of both vaccination and measles seven had been vaccinated after developing measles and the other one only 20 days before. There were two non-SSPE patients with documented dates of receiving measles vaccine twice, who subsequently developed measles. Loss of vaccine potency due to cold chain failure is the likely explanation for these and other vaccine failures.

In order to attain effective protection through measles immunization the vaccine used should maintain its potency until it is given. To avoid interference with maternal antibodies and wastage, measles vaccination should be given after maternal antibodies have disappeared and before the acquisition of natural measles infection. For effective measles control in a population, sustained vaccination coverage over 90% is required [30]. In PNG, mass immunization against measles was introduced in 1982 [31, 32]. This initially included routine vaccination at 9 months of age. Subsequently, in 1990, following a study which showed declining maternal antibodies and an adequate response to measles vaccine from 4 months of age [32], routine vaccination was carried out at 6 months of age with a booster at 9 months. In addition, an intensive immunization policy has been promoted that recommends the vaccination of all children during epidemics and all unvaccinated children between 6 months and 3 years when admitted to hospitals [31]. Despite this policy measles vaccination coverage of children below 1 year of age in EHP for the years 1989–1996 fluctuated between 7 and 71% [26, 33, 34] whereas coverage of 6-month-old infants for 1996–2000 was between 46 and 82% and for 9-month-old infants between 37 and 78% (Provincial reports on 28 June 2001 from the Papua New Guinea Department of Health). Moreover, the inadequate cold-chain system, known to be a major problem in PNG [35], must also have lowered the actual effective vaccination rate and led to the inoculation of ineffective vaccine in some children. Reported total annual hospital admissions for measles decreased steadily after 1993 to the lowest level in 1997 throughout PNG including EHP [33, 34]. However, GBGH had experienced measles epidemics in 1982, 1986, 1988–1989 and 1992, and a large and extended one occurred in 1998 [36–38].

Low vaccination coverage and cold chain system failure hamper measles control. Overcrowded dwelling conditions facilitate the spread of measles. Improper timing of vaccination also diminishes the effectiveness of vaccination. Most developing countries including PNG have all these problems in common. However, although developing countries other than PNG have reported a high incidence of SSPE [15, 16, 18] in none has the disease occurred to the same extent as in EHP. Similarly, the previously reported high incidences from developed countries in the prevaccine era [14, 15] or in the years before the influence of mass immunization did appear as a sharp decline in incidence of new cases [10] are much lower than that observed in this study. Comparison with the prevaccine era in PNG is not possible. In the 1970s

measles was not a problem in PNG, to the extent that the paediatricians resisted the introduction of measles vaccination. In 1981 PNG had its first serious measles outbreak and measles vaccination began in 1982. There was then no known SSPE. We expect, therefore, that unexplained local factors are responsible for this unusually high incidence of SSPE in EHP. Possibly, there is local circulating MV with high neurotropism or other peculiarity and/or genetically determined high-affinity MV receptors in the brain. There may also be some other local factors that enhance persistent infection. These include a modified cell-mediated immunity that has been previously reported in this region [39]. Neither of the two amplified nucleotide sequences of measles virus was identical to any vaccine strain [21] and there was no evidence to implicate measles vaccination in the pathogenesis. In an ongoing case-control study on measles vaccination and illness we aim to identify these local factors and evaluate the involved risks. Further studies, virological and immunological, using proper controls are crucial for such evaluation.

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Appendix 1. *History of measles vaccination and illness among SSPE patients*

	Number of patients					
	Documentation of measles vaccination					
Status	Available			Unavailable		
Vaccinated (33)	19			14		
Had measles (15)		10			5	
Documented			8			0
Undocumented			2			5
Did not have measles (13)		7			6	
Documented			7			0
Undocumented			0			6
Measles uncertain or not studied (5)		2			3	
Unvaccinated (4)	2			2		
Had measles (1)		0			1	
Undocumented			0			1
Did not have measles (2)		2			0	
Documented			2			0
Measles uncertain or not studied (1)		0			1	
Subtotal	21			16		
Measles vaccination uncertain or not studied (15)			15			
Had measles (4)						
Did not have measles (4)						
Measles uncertain or not studied (7)						
Total			52*			

* The status of measles vaccination and disease was unknown in three patients.

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Appendix 2. *Summarized information of the demography, clinical features and laboratory findings in the 80 patients enrolled in the study*

Serial No.	Gender & age in years	Diagnosis when registered	Jerks and/or falls	Typical PSD[†]	EIA value of undiluted CSF	EIA value of undiluted serum	MV[$] genome from PBMC[$$]	Final diagnosis	Birth [(year – 1900) /month]	H/o 1st MVa[#]	Date of 1st MVa [(year – 1900)/ month/day]	Dates of 2nd and 3rd MVas [(year – 1900)/ month/day]	H/o M[##]	Date of M [(year – 1900)/ month/day]	Time from SSPE onset to registration	Registration [(year – 1900)/ month]
50	F9·6	S[α]	+		10 400	496 000	–	*S*[a]	88/11	A	89/9/11		B*		(4 d)[&&]	98/6
32	M7·7	S	+		11 200	390 000	–	*S*	90/3	A	92/7/16	95/4/12	A*	91/5/31	(17 d)	97/11
68	M6·9	S	+		12 840	444 000		*S*	87/3	A	92/11/13	93/2/16	B*		(10 d)	98/11
22	F4·3	S	+		14 680	532 000	+	*S*	93/5	A	93/9/22	94/6/14	C*		(6 w)	97/9
77	F5·1	S	+		14 700	606 000		*S*	(93/11)[&&]	C			D*		(1 m)	99/2
27	M14·8	S	+		16 560	356 000	–	*S*	(82/11)	C			C*		(4 w)	97/10
10	F9·8	S	+		16 840	970 000		*S*	(87/3)	E			E*		(6 m)	97/6
42	F2·8	S	+		17 620	560 000	–	*S*	95/3	B			B*		(4 w)	98/2
36	F6·8	S	+	–	18 400	628 000	–	*S*	91/3	A	91/8/15	91/9/29	C*		(11 d)	98/1
3	F8·7	S	+		19 200	388 000		*S*	(89/1)	E			C*		(7 m)	98/4
69	F4·4	S	+	+	20 000	622 000		*S*	91/12	E			C*		(3 m)	98/12
43	F5·2	S	+		21 600	740 000	–	*S*	(92/12)	C			D*		(7 w)	98/3
46	F9·0	S	+		23 200	640 000		*S*	(88/9)	C			C*		(5 m)	98/4
54	MUdtm.[h] age	OND[f]	+		24 800	584 000		*S*	(88/4)	E			D*		(0 y ~ 10 y)	98/3
52	F6·3	S	+		24 800	1 396 000		*S*	(92/2)	C			E*		(2 w)	98/6
7	M7·0	S	+		25 400	380 000		*S*	90/1	A	90/10/8	95/7/31	A*	90/10/28	(5 w)	97/5
20	M1·9	S	+	Unsure	27 200	596 000	–	*S*	85/9	A	86/7/21		A*	86/7/6	(4 w)	97/9
58	M12·7	S	+		28 000	632 000		*S*	(85/10)	C			D*		(3 m)	98/9
62	M10	S	+		29 600	1 072 000		*S*	92/6	E			E*		(1 m)	98/10
21	M5·0	S	+		33 000	650 000	–	*S*	(92/9)	E			D*		(4 w)	97/9
70	M7·5	S	+		35 800	722 000		*S*	(90/12)	C			C*		(1·5 y)	99/1
24	M5·1	S	+		35 400	1 028 000		*S*	(91/11)	F			F*		(3 m 2 w)	97/2
76	M13·1	S	+	+	36 200	466 000		*S*	92/4	E			D*		(6 w)	99/2
53	M6·3	S	+		38 400	534 000		*S*	(92/1)	C			D*		(1 m)	98/6
31	M5·9	S	+		39 000	480 000	–	*S*	91/12	A	92/6/22	95/10/9	A*	92/6/15	(1 w)	97/11
14	M5·2	S	+		40 480	1 308 000		*S*	(92/4)	C			C*		(1 m)	97/7
73	F4·9	S	+		41 000	642 000		*S*	92/5	F			B*		(2 m)	99/1
26	M11·2	S	+		41 200	750 000	–	*S*	(86/5)	C			E*		(3 m)	97/10
81	M9·3	S	+	+	42 800	720 000		*S*	91/10	C			D*		(2 m)	99/3
74	F6·7	S	+	Unsure	51 600	786 000		*S*	(92/12)	A	{92/11/19}[¥]	{95/8/6, 97/10/28[&]}[¥]	E*		(2 m)	99/3
67	F11·3	S	+		52 400	632 000		*S*	87/3	A	98/8/23		B*		(2 m)	98/9
56	M3·3	S	+		53 600	1 690 000		*S*	95/6	A	95/12/20		F*		(1 m)	98/9

47	FX	S	+		55 200	656 000	–	*S*	X	X			X		(2 m)	98/9
28	F8·6	S	+		55 400	604 000	–	*S*	(88/3)	C			C*		(19 d)	97/10
23	M4·8	S	+	+	55 480	778 000	+	*S*	92/11	A	93/5/27	93/9/2	A*	93/5/? Before 1st MV	(5 d)	97/9
4	M11·5	S	+		56 000	788 000		*S*	85/10	B			B*		(3 w)	97/4
80	F7·2	S	+	Unsure	71 600	1 672 000		*S*	91/10	A	92/8/11	92/12/14	A*	92/6/21	(3 m)	99/4
39	F11·3	OND	+		78 000	1 812 000	–	*S*	(86/11)	C			D*		(4 m)	98/2
17	M7·0	S	+		83 200	498 000	–	*S*	(89/1)	C			E*		(1 y 3 m)	97/4
75	M6·7	S	+		130 400	1 228 000		*S*	92/4	A	93/1/12	94/3/24, 95/6/13[&]	B*		(2 m)	99/2
25	F11·5	S	+		200[‡]	6400[‡]		*S*	85/8	A	86/8/?	86/11/?	B*		(8 m)	97/9
16	M9·4	S	+		1900	552 000	–	*PS*[b]	87/8	A	92/7/19		A*	88/2/?	(2 m)	97/3
33	?X	S			5200	154 000	–	*PS*	X	X			X		X	97/11 ~ 97/12
35	F10·0	S	+		5200	186 000		*PS*	(87/10)	D			E*		(3 m)	98/1
8	F5·8	S	+		33 600			*PS*	(86/9)	F			C*		(3 y ~ 4 y)	97/4
71	M5·6	S	Udtm.		34 000	75 000		*PS*	(90/10)	E			C*		(1·5 y)	99/1
65	MX	S			41 200	644 000		*PS*	X	X			X		X	98/10 ~ 98/11
12	M6·7	S	Udtm.		50 800	1 146 000		*PS*	(90/4)	E			E*		(7 m)	97/7
51	FUdtm. age	S			60 800	1 684 000		*PS*	88/11	F			F*		(0 y ~ 6 y)	95/4
37	M3·3	S	+	Unsure	78 000	196 000		*PS*	(94/7)	D			C*		(2 m)	98/1
15	F9·3	S	+			123 200		*PS*	(88/5)	E			E*		(3 w)	97/8
13	M6·7	S	+			149 200		*PS*	90/11	A	92/5/26	95/5/31	B*		(1 m)	97/7
6	F5·8	S	+			344 000		*PS*	91/8	A	92/8/1	93/4/27	A*	92/7/19	(21 d)	97/5
48	M12·6	S	+			584 000		*PS*	85/9	A	88/6/15		B*		(3 w)	98/5
49	M5·3	S	+			876 000		*PS*	85/9	E			E*		(8 d)	98/4
78	F10·7	S	–		< 40	1020		*DNS*[c]	(88/6)	C			D*		(6 w)	99/2
64	M5·3	AM[g]			< 40	1020		*DNS*	Y	Y			Y		Y	98/10 ~ 98/11
41	M6·1	OND			< 40	1280		*DNS*	(92/1)	E			E*		(0 y ~ 5 y)	98/2
45	FX	S			< 40	2380		*DNS*	X	X			X		X	98/3 ~ 98/4
2	M4·8	S	Udtm.		< 40	4600		*DNS*	(91/12)	E			C*		(4 w)	93/3
5	M12·3	S			< 40			*DNS*	X	X			X		X	97/4 ~ 97/5
66	?X	M[g]			< 40			*DNS*	Y	Y			Y		Y	98/10 ~ 98/11
30	F0·75	AM				< 400		*DNS*	92·2	B			A*	97/10/?	AM	97/11
79	M0·34	AM				< 400		*DNS*	(98/10)	E			A*	{99/2/15}	AM	99/2
19	M4·3	S			40	6660	–	*PNS*[d]	X	X			X		X	97/8 ~ 97/9
40	F5·1	OND			74	2380		*PNS*	93/1	A	93/8/12	93/9/9	B*		(0 ~ 5 y)	98/2
61	M6·3	OND	+		82	1580		*PNS*	92/6	A	93/6/4	93/7/7	A*	93/8/24	(1 y)	98/10
34	M4·6	AM			88	1580		*PNS*	93/5	A	93/12/1	94/3/29	A*	97/12/14	(1 y)	97/12
63	F0·33	AM				620		*PNS*	(98/6)	E			A*	{98/10/30}	AM	98/10
60	M5·3	AM				2960		*PNS*	Y	Y			Y		Y	98/10
38	M1·3	AM				3740		*PNS*	(96/10)	E			C*		AM	98/1

Appendix 2 (*cont.*)

Serial No.	Gender & age in years	Diagnosis when registered	Jerks and/or falls	Typical PSD[†]	EIA value of undiluted CSF	EIA value of undiluted serum	MV[$] genome from PBMC[$$]	Final diagnosis	Birth [(year – 1900) /month]	H/o 1st MVa[#]	Date of 1st MVa [(year – 1900)/ month/day]	Dates of 2nd and 3rd MVas [(year – 1900)/ month/day]	H/o M[##]	Date of M [(year – 1900)/ month/day]	Time from SSPE onset to registration	Registration [(year – 1900)/ month]
57	MX	AM				6020		*PNS*	95/4	X			X		X	98/9
29	M3·3	PM[g]				7660		*PNS*	(94/7)	B			A*		AM	97/10
11	MX	S				8280		*PNS*	X	X			X		X	97/6∼97/7
55	M3·3	M[g]				15 960		*PNS*	95/6	C			A*	{98/9/?}	AM	98/9
59	F9·2	S	+	Uncertain	58	38 000		*I*[e]	(89/8)	C			E*		(3 w)	98/10
72	6·7	S			65 000			*I*	92/5	A	95/10/13		B*		(1 y)	99/1
18	F10·3	S				66 000		*I*	X	X			X		X	97/8∼97/9
1	F5·3	S	+					*I*	(92/1)	E			C*		(3 m)	97/4
9	X	S						*I*	X	X			X		X	97/4∼97/6

[†] PSD, periodic synchronous discharge. [$] MV, measles virus. [$$] PBMC, peripheral blood mononuclear cells. [#] MVa, measles vaccination. [##] M, measles. [α] S, presumptive SSPE, [a] *S*, *SSPE*. [b] *PS*, *probable SSPE*. [c] *DNS*, *definitely not SSPE*. [d] *PNS*, *probably not SSPE*. [e] *I*, *inconclusive of whether SSPE or not*. [f] OND, other neurological disease. [g] AM, M and PM, acute measles, measles and post-measles, respectively. [h] Udtm., undetermined. [‡] Estimated not at SRL, so the titre incomparable to the EIA value but highly positive. [&] 3rd MVa. [&&] The information in parentheses ( ) solely depended on parents' statement. [¥] The information in parentheses { } documented in other sources than the child health record book (CHRB). A and A*, documented. B and B*, not documented. C and C*, documentation unavailable. D and D*, child health records book or other documented source of information unavailable. E and E*, uncertain. F, not asked for. X, case protocol misplaced. Y, not investigated because the patient had acute or post-measles illness but no neurological problems. This table supplies only information substantiated by documentation except the year of birth in some patients and the time interval between the development of SSPE and registration (i.e. enrollment) in the study.

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