MAJOR ARTICLE

Subacute Sclerosing Panencephalitis: More Cases of This Fatal Disease Are Prevented by Measles Immunization than Was Previously Recognized

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(See the editorial commentary by Katz, on pages 1679–80.)

Background. The most severe sequela of measles virus infection is subacute sclerosing panencephalitis (SSPE), a fatal disease of the central nervous system that generally develops 7–10 years after infection. From 1989 through 1991, a resurgence of measles occurred in the United States, with 55,622 cases of measles reported. The purpose of the present study was to identify cases of SSPE that were associated with the resurgence of measles and to calculate the risk of developing SSPE.

Methods. Brain tissue samples obtained from 11 patients with a presumptive diagnosis of SSPE were tested for the presence of measles virus RNA. Measles virus genotypes were determined by reverse-transcription polymerase chain reaction (RT-PCR) and by analysis of the sequences of the PCR products. A search of the literature was conducted to identify reports of cases of SSPE in persons residing in the United States who had measles during 1989–1991.

Results. The measles virus sequences derived from brain tissue samples obtained from 11 patients with SSPE confirmed the diagnosis of SSPE. For 5 of the 11 patients with SSPE who had samples tested by RT-PCR and for 7 patients with SSPE who were identified in published case reports, it was determined that the development of SSPE was associated with the measles resurgence that occurred in the United States during 1989–1991. The estimated risk of developing SSPE was 10-fold higher than the previous estimate reported for the United States in 1982.

Conclusions. Vaccination against measles prevents more cases of SSPE than was originally estimated.

Subacute sclerosing panencephalitis (SSPE) is a progressive fatal disease of the central nervous system that is caused by a persistent measles virus infection. Early clinical characteristics of SSPE may be variable, but they often include behavioral changes, cognitive deterioration, sporadic episodes of falling, and such optic disturbances as chorioretinitis [1, 2]. As the disease advances, neurologic symptoms, such as myoclonic jerks or spasms, become more pronounced, and the patient develops severe physical and mental impairment. SSPE has an average period of latency of 7–10 years (range, 1 month to 27 years) after measles virus infection, and death generally occurs ~1–3 years after the onset of symptoms. There are known risk factors for SSPE, such as the development of measles virus infection at an early age (i.e., before 2 years of age), and most studies have noted that a greater proportion of cases of SSPE occur among males. The reason why measles virus persists in some individuals and results in deadly consequences is unknown, but it is likely to be host related [3].

Although measles is a monotypic virus, 22 genotypes of wild-type virus are recognized; many genotypes have been associated with endemic circulation of measles virus in certain geographic regions or have been documented in connection with an outbreak or epidemic in an area [4, 5]. The measles vaccine virus strains belong to genotype A and can be distinguished from

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wild-type virus of the same genotype by means of sequence analysis [6–8]. Analyses of measles virus sequences in brain tissue samples obtained from patients with SSPE have identified only wild-type measles virus, and the virus genotypes identified have been consistent with the genotype of measles virus that circulated in the area where the patients lived and to which the patients had been exposed ⩾10 years before the onset of symptoms of SSPE [6, 9–13]. Genetic studies have supported epidemiologic evidence that measles vaccine virus does not cause SSPE [6, 14, 15]. In cases of SSPE that developed in children or adults who had no history of measles but who did have a history of vaccination against measles virus, analysis of measles virus sequences derived from the patients confirmed the presence of the wild-type genome, indicating that the individuals had an undiagnosed measles virus infection [6, 7, 9].

In the United States, it was estimated that the average risk of developing SSPE was 8.5 cases of SSPE/1 million cases of measles that occurred during 1960–1974, under the assumption that only 1 in 10 cases of measles was reported [16, 17]. By the late 1980s, the number of reported cases of SSPE had decreased to 1–2 cases/year (from a high of 40–50 reported cases/year in the 1970s), on the basis of the number of cases reported to a registry of SSPE cases that was established in 1969 [18, 19]. The observed decrease in the number of SSPE cases in the late 1980s occurred after a period during which the incidence of measles was low (1981–1988), with an average total number of 3000 cases of measles reported annually [20].

Decreasing rates of vaccination in the United States, particularly among preschool-aged children (children <5 years of age) living in inner-city areas, resulted in a resurgence in the number of cases of measles reported during 1989–1991; during this period, 55,622 cases of measles and 123 measles-associated deaths were reported [21]. The virus genotype associated with measles cases investigated during the period of measles resurgence was genotype D3 [22]. In response to the measles epidemic that occurred in the United States, additional measures were implemented to eliminate the transmission of measles, including the adoption of a 2-dose schedule of measles vaccine administration. As a result, only 312 cases of measles were reported, and measles virus of genotype D3 has not been isolated from individuals whose infection was classified as an indigenous measles case in the United States since March 1992 [22, 23]. In 2000, a panel of experts examined measles surveillance data and concluded that elimination of endemic measles in the United States had been achieved [24].

In the present study, we analyzed measles virus sequences that were identified in brain biopsy specimens or in material obtained at autopsy from patients with SSPE and that were then submitted to the Centers for Disease Control and Prevention (CDC) from 1992 through 2003. Although most of the specimens were submitted to the CDC because the patients lacked a history of measles but had a positive history of vaccination, we identified only wild-type measles virus in the patients' specimens. We calculated the risk of developing SSPE due to measles acquired during the period of measles resurgence in the United States, by use of data for the patient subset that included patients with SSPE from our genetic study who were determined to have had measles during 1989–1991 and patients with SSPE who were identified in case reports as having had probable cases of measles in the United States during 1989–1991. The risk of SSPE estimated in this study suggests that prevention of measles cases through vaccination may prevent more cases of SSPE than was previously recognized.

PATIENTS, MATERIALS, AND METHODS

Patients with SSPE. Eleven patients with either a confirmed or a presumptive diagnosis of SSPE were referred to the CDC, and brain tissue specimens obtained from these patients were submitted for detection of measles virus RNA and for analysis of measles virus sequences. Diagnosis of SSPE was based on the presence of clinical characteristics consistent with SSPE and was confirmed by either the referring institution or the CDC when ⩾2 of the following laboratory criteria were present: (1) an electroencephalographic pattern characteristic of SSPE, (2) the presence of typical histopathologic changes in neurologic tissues derived at autopsy or from brain biopsy specimens (in particular, intranuclear and cytoplasmic inclusion bodies in neurons and glial cells), (3) detection of elevated levels of measles antibody in cerebrospinal fluid, and (4) identification of measles virus RNA or antigen in brain tissues by means of reverse-transcription polymerase chain reaction (RT-PCR) or immunohistochemical analysis [25].

Additional patients in the United States who had SSPE and who had probable acute infection during 1989–1991 were identified through a search of the literature for case reports of SSPE in the United States. Data from case reports that provided patient information that was adequate to assess whether the patient had measles or rash during 1989–1991 in the United States were included in the results. The authors of 3 of the case reports were contacted for additional information that would allow for confirmation of a patient's location or date of birth. All of the case reports included information on the supporting laboratory and clinical criteria used in the diagnosis of SSPE.

Detection and analysis of measles virus genome from brain specimens. Specimens that underwent RT-PCR and sequencing included fresh-frozen, paraffin-embedded, or formalin-fixed brain tissue specimens that had been obtained after death or during biopsy. RNA was extracted from paraffin-embedded tissue samples according to the procedure described by Koopmans et al. [26]. RNA was extracted from fresh-frozen or formalin-fixed brain tissue by use of the guanidinium-acid phenol meth-

Table 1. Patients with subacute sclerosing panencephalitis (SSPE) who were referred to the Centers for Disease Control and Prevention (CDC) and whose SSPE cases were associated with measles virus infection acquired in the United States during 1989–1991.

Patient	Year[a] of referral to the CDC (patient age at referral, years)	Patient's year of birth, sex	History of measles or rash	Patient location[b]	History of vaccination[c]	Genotype of measles virus identified
1	1996 (5)	1991, F	NR	Georgia	Yes	D3
2	1998 (9)	1989, M	NR	Texas	Yes	D3
3	1998 (7)	1991, F	NR	Texas	Yes	D3
4	2001 (11)	1990, F	NR	Florida	Yes	D3
5	2002 (12)	1990, M	Rash[d]	California	Yes	D3

NOTE. NR, not reported.

[a] The year of onset of SSPE was not available for all patients and may not be the same as the year of referral given here.
[b] Location where patient resided during childhood or state of residence at the time of referral.
[c] Patient age at vaccination was known only for patient 4. Patient 4 was vaccinated at 1 and 5 years of age.
[d] Patient 5 developed rash at 8 months of age.

od [27] with minor modifications. By use of a sterile scalpel, the tissue samples were cut into slices that measured ~3 × 3 × 3 mm, and they were immediately placed into 500 μL of guanidinium isothiocyanate buffer and were minced with a sterile scalpel or a 22-gauge needle. Insoluble material was removed by centrifugation at 1500 *g* for 15 min at 4°C. The supernatant was then acidified and extracted using phenol-chloroform [27]. The RNA pellet was resuspended in 30 μL of RNase-free water, and the RNA concentration was determined by ultraviolet spectroscopy.

RT-PCR and sequence analysis. To prepare templates for sequencing, RT-PCR was performed using the Superscript One Step RT-PCR kit (Gibco BRL), as described elsewhere [28]. Primers were designed to amplify the 450 nucleotides coding for the COOH-terminal 150 amino acids of the nucleoprotein [8]. PCR products were purified using the PCR Preps DNA Purification System (Promega) and were analyzed by agarose gel electrophoresis followed by ethidium bromide staining. Templates were sequenced using a cycle sequencing reaction with fluorescent dye terminators (Applied Biosystems Division, Perkin-Elmer), and the reaction products were analyzed using an ABI 3100 automatic sequencer (Applied Biosystems Division, Perkin-Elmer). Sequence data from multiple reactions were analyzed using the Genetics Computer Group Package (version 10.1; Accelrys) [29].

The PCR primers used in the RT-PCR are known to amplify all genotypes of measles virus, including the vaccine virus strains [4, 8]. Genotypes were assigned using phylogenetic analysis using parsimony [30], to compare the sequences derived from the brain specimens with reference sequences that represent the 22 genotypes of measles virus as designated by the World Health Organization [4].

RESULTS

Measles virus RNA was detected in brain tissue samples obtained from 11 patients with SSPE who were referred to the CDC during 1992–2003, and virus genotypes were assigned after sequence analysis of the PCR products was performed (tables 1 and 2). Measles virus antigen was detected in 2 of the brain tissue specimens by use of immunohistochemical analysis (data not shown). The age range of the patients was 5–36 years (mean age, 14 years). Genotype E was identified in samples obtained from the 2 patients who were >20 years of age at the time of referral (table 2, patients 7 and 11). Genotype D5 was identified in a sample obtained from a child who had resided in Okinawa City, Japan, during infancy (table 2, patient 8). Genotype C1 was identified in a sample obtained from a child (table 2, patient 6) who had a history of acute measles in 1977. All of the patients listed in table 1, as well as 2 of the patients listed in table 2 (patients 9 and 10), were found to have been infected with measles virus of genotype D3.

The SSPE cases of the patients listed in table 1 were associated with measles virus infection that occurred during the 1989–1991 measles epidemic, because all of these patients with SSPE were born and resided in the United States during 1989–1991 and because the brain tissue samples obtained from these patients yielded virus sequences that corresponded to the wild-type measles virus genotype associated with the outbreak (i.e., genotype D3), thus confirming that the patients developed SSPE as a result of an undiagnosed infection with measles virus that occurred during the epidemic. Without the genotype information, the SSPE cases of the patients who did not have a history of measles virus infection could not have been associated with the measles resurgence that occurred during 1989–

Table 2. Patients with subacute sclerosing panencephalitis who were referred to the Centers for Disease Control and Prevention (CDC) and who had measles virus of the wild-type genotype identified in brain tissue samples, although the genotype or patient location ruled out an association with measles acquired in the United States during 1989–1991.

Patient	Year[a] of referral to the CDC (patient age at referral, years)	Patient's year of birth, sex	History of measles or rash, year of occurrence (patient age)	Patient location[b]	History of vaccination (patient age at vaccination, if known)	Genotype of measles virus identified
6	1992 (16)	1976, M	Measles, 1977 (12 months)	Wisconsin	No	C1
7	1993 (28)	1965, M	Measles, 1968 (3 years)	Wisconsin	Yes (12 years)	E
8	1995 (5)	1990, M	Rash, 1991 (15 months)	Ohio[c]	Yes (17 months)	D5
9	1999 (8)	1990, M	Measles, 1991 (7 months)	Puerto Rico	No	D3
10	2001 (16)	1985, M	NR	Nicaragua[d]	Yes (15 years)	D3
11	2003 (36)	1967, M	NR	Illinois	Yes	E

NOTE. NR, not reported.

[a] The year of onset of symptoms of subacute sclerosing panencephalitis was not available for all patients and may not be the same as the year of referral given here.

[b] Location where patient resided during childhood or state of residence at the time of referral.

[c] Patient 8 lived in Okinawa City, Japan, from 5 months of age until ~2 years of age.

[d] Patient 10 lived in Florida after 15 years of age.

1991, because the possibility of SSPE developing as a result of receipt of the measles vaccine could not have been ruled out.

Seven additional patients in the United States who had SSPE and a history of measles or rash during 1989–1991 were identified from case reports [31–36] (table 3). All of these patients with SSPE were born during or just before the 3-year period of the resurgence of measles. The patients had a history of measles or rash during that period and lived in California, Pennsylvania, or New York—states that were known to have large numbers of measles cases. In addition, 1 of the case reports (that of Baram et al. [34]) included measles virus sequence data, but the virus genotype had not been identified. We analyzed the published sequence and identified the genotype as D3 (data not shown).

The risk of developing SSPE as a result of measles virus infection that occurred during 1989–1991 can be calculated by using as the denominator the 55,622 measles cases reported during the 3-year period of measles resurgence. The 12 cases of SSPE in the patients identified in the present study (tables 1 and 3) that developed from measles acquired during 1989–1991 were used as the numerator. Therefore, the estimated risk of SSPE was 12 cases of SSPE/55,622 reported cases of measles, or 22 cases of SSPE/100,000 reported cases of measles.

DISCUSSION

The measles virus genotypes detected in brain tissue specimens obtained from patients with SSPE in the present study represented wild-type viruses (tables 1 and 2). Therefore, the patients with SSPE who did not have a history of measles either had a subclinical measles virus infection or an undiagnosed case of measles. For example, 1 patient (table 2, patient 8), who, during infancy, had resided in Okinawa City, had a history of measles vaccination at 17 months of age but had no record of having had measles. However, the medical history of this patient included a febrile illness with rash that occurred at 15 months of age and that was described as "roseola"; the occurrence of this rash coincided with the time that the patient spent in Japan and is consistent with the identification of virus of genotype D5, which is known to have been circulating in Japan in the early 1990s [37]. Our data support previous epidemiologic and genetic studies that found no evidence that measles vaccine virus can cause SSPE [6, 9, 14, 15].

The genotypes of measles virus identified in brain tissue samples obtained from the patients with SSPE who were aged 16, 28, and 36 years at the time of referral (table 2; patients 6, 7, and 11, respectively) provide information about the circulation of measles viruses in the United States during the 1960s and 1970s, when few viruses were being isolated and characterized. The results suggest that genotype C1 circulated in the late 1970s (patient 6) and that genotype E was present in the late 1960s or 1970s (patients 7 and 11). Genotype E, which was first detected in Germany in 1971, has not been found since 1987, and this lineage of measles virus is considered to be inactive [4, 38, 39].

Identification of 12 cases of SSPE associated with measles virus infection that occurred during 1989–1991 (tables 1 and 3) suggests that the risk of SSPE determined using data available in 1982—that is, 8.5 cases of SSPE/1 million cases of measles—may have underestimated the true risk of SSPE. The resurgence of measles in 1989 was preceded by several years during which the incidence of measles was low, and the years after the re-

Table 3. Additional patients with subacute sclerosing panencephalitis who had a history of measles or rash during 1989–1991 in the United States, as identified from case reports.

Reference, patient	Patient age at diagnosis	Sex	History of measles or rash, year of occurrence (patient age)	Patient location	History of vaccination (patient age at vaccination, if known)
[31]	4.5 years	M	Measles, 1991 (8 months)	Philadelphia, PA	Yes (15 months)
[32]	9 years	F	Measles, 1989 (1 year)	California	Yes (1 year and 5 years)
[33]					
2	10 years	M	Rash, 1989/1990 (3 months)	California	NR
5	13 years	F	Rash, 1989/1990 (11 months)	California	NR
[34]	22 months	F	Rash,[a] 1990 (5 weeks)	California	Yes (18 months)
[35]	5.5 years	M	Measles, 1991 (3 years)	Brooklyn, NY	Yes (1 year)
[36]	4 years	F	Measles, 1990 (3 months)	Bronx, NY	Yes (15 months)

NOTE. NR, not reported.

[a] The measles virus sequence reported in a study by Baram et al. [34] was determined to be measles virus of genotype D3.

surgence were remarkable for the record low numbers of measles cases reported. This unique epidemiologic situation, together with the ongoing surveillance for cases of measles and the determination of the genotype involved in the epidemic (genotype D3), was critical in the calculation of a revised estimate of the risk of SSPE [23, 40, 41]. The higher estimated risk of SSPE reported in the present study, compared with the previously estimated risk, could be the result of the different methods used to identify SSPE cases, the underreporting of measles cases during 1989–1991, the higher incidence of measles during the period of resurgence of measles in the population at greatest risk for SSPE (i.e., children <5 years age), or the observation that viruses of genotype D3 are more likely to cause SSPE. Each of these reasons is discussed below.

In the present study, sources of SSPE cases were limited to patients with SSPE who were referred to the CDC or to case reports of SSPE that could be associated with measles virus infection that occurred during 1989–1991. Both sources of data existed because of a diagnostic dilemma (e.g., no history of measles), an unusual presentation of SSPE, or a report of a novel use of diagnostic tools in association with a case of SSPE. The true number of SSPE cases that developed after the resurgence of measles in 1989–1991 is likely to be greater than the 12 cases used in the calculation of our estimate of the risk of SSPE. Data collected from epidemiologic surveys of SSPE in several countries, including the United States [15, 17, 42–45], indicated that the majority (72%–84%) of patients with SSPE had a history of measles. Only 4 (33%) of the 12 patients with SSPE who are listed in tables 1 and 3 and whose cases of SSPE were associated with infection that occurred during the period of measles resurgence had a history of measles.

In addition, examination of reports of cases of SSPE provided to the USA/International SSPE Registry (P.R.D., unpublished data) revealed as many as 10 additional SSPE cases that were temporally associated with measles virus infection that occurred during 1989–1991, after exclusion of patients with SSPE whose case report data suggested a possible duplication of the data for a patient identified in the present study. The cases of SSPE reported to the USA/International SSPE Registry were not included in our risk estimate because of uncertainty about the location of the patients at the time that the acute infection developed. During the years of measles resurgence in the United States, there was a concurrent outbreak of measles throughout the Western Hemisphere, including Mexico. Because of the scrutiny of the medical history and demographic characteristics of the patients with SSPE referred to the CDC and of the patients included in the published case reports, sufficient information could be obtained to reliably conclude that the patients had developed SSPE as a result of exposure to measles in the United States during 1989–1991.

There are few studies available to assess the completeness of reporting of measles cases during 1989–1991, and those studies evaluate the efficiency, or completeness, of reporting probable cases of measles to local health departments [46]. Measles is a notifiable disease, and all states require physicians to report suspected cases of measles. In a hospital-based study conducted in Los Angeles in 1989, 51% of physician-diagnosed cases of measles were reported to the local or state health department [47]. However, identification of probable cases of measles is based on clinical suspicion of measles, as identified by a search of hospital discharge records or of patient records in private practices, and such cases are generally not laboratory confirmed, particularly during an epidemic. A community-based study conducted in Los Angeles to evaluate cases of measles reported during 1990–1991 found that 29% of probable cases of measles among children, as recalled by parents, were reported [48].

To reflect the underreporting of measles cases during 1989–1991, the risk of SSPE can be adjusted using an estimated range

of reporting efficiency based on the studies cited above. If 30%–50% of measles cases were reported, the revised risk of SSPE would then be 6.5–11 cases of SSPE/100,000 cases of measles, which is 7–13 times higher than the estimated risk of SSPE associated with measles cases that occurred in the United States during 1960–1974. The higher risk estimated in the present study is comparable to the risk estimated in Miller and colleagues' report [49] of the risk of SSPE among children in England in Wales who, before 2 years of age, were infected with measles virus during 1960–1989 (6.8−18 cases of SSPE/100,000 cases of measles).

In contrast, the number of measles cases used as the denominator in the calculation of the estimated risk of SSPE in the United States in 1982 may have resulted in overestimation of the number of measles cases that occurred during 1960–1974. It was inferred that only 1 of every 10 cases of measles was reported before vaccine licensure in 1963, because no more than 400,000–500,000 cases were reported per year, and the actual number of cases that occurred annually was expected to correspond to the size of the birth cohort (~4 million) [16, 50]. However, in the calculation of the risk estimate, a 10% rate of reporting efficiency was applied to the annual number of reported cases for each year from 1960 through 1974, a period during which the rate of reporting efficiency had likely improved because of both the decreasing incidence of measles and the announcement of the first goal of measles elimination in 1967 [16, 22, 50]. No adjustment was made to the number of cases of SSPE, to correct for possible underreporting of the number of SSPE cases to the National Registry for SSPE [16].

There were no studies to ascertain the completeness of the reporting of SSPE cases to the National Registry for SSPE, which was used to determine the number of SSPE cases for the calculation of the SSPE risk estimate in 1982 [14, 16]. The SSPE Registry was established in 1969 and was maintained at the University of Tennessee (Memphis) until 1980 [18, 19], although it was never considered to be complete. SSPE cases were reported to the National Registry for SSPE primarily by members of the Child Neurology Society, and additional data were collected via questionnaires or surveys directed to pediatric neurologists [17, 18, 51]. In addition to having been underreported, many cases of SSPE likely were undiagnosed, because relatively little was known about the various clinical presentations of SSPE [19]. Diagnosis depended on a high index of suspicion, as well as patient access to either specialized neurologists or a physician familiar with the rare disease SSPE. The numerous case reports and reviews of SSPE underscore the complexity of the clinical aspects of the disease and the challenges associated with the recognition and diagnosis of SSPE, particularly adult-onset SSPE and SSPE that follows a fulminating course [1, 2, 19, 52, 53].

The risk of SSPE calculated in the present study may be higher than the risk estimated for the period 1960–1974, in part because of the large number of cases of measles that occurred in young children during the 1989–1991 epidemic. It was noted that, in 1989 and 1990, the proportion of cases among children <5 years of age exceeded the proportion among school-aged children (children 5–19 years of age) for the first time since such detailed information became available in 1973 [54]. In 1990, the highest incidence rates were among children <1 year of age (119.3 cases of measles/100,000 children) and among children 1–4 years of age (58.3 cases of measles/100,000 children). Because the age-specific incidence of measles was not available for the period 1960–1974, we cannot evaluate the influence of the high incidence of measles in young children during 1989–1991 on the risk estimate presented in this report. However, in this study, US-born patients with SSPE who had genotype D3 virus sequences identified in brain tissue samples (table 1) were all born during the years of the measles resurgence and presumably were infected during their first 2 years of life.

There is no evidence to suggest that infection with measles virus of the D3 genotype would increase the risk of subsequent development of SSPE. Genotype assignments are based on sequence variation in wild-type viruses, but there are no known biological differences between the genotypes. Many of the recognized genotypes have been detected in brain tissue samples obtained from patients with SSPE; the genotype detected has been consistent with the genotype that was circulating when the patient experienced the acute infection [9–13]. For example, in 2003, measles virus of genotype D6 was identified in 8 Argentine children with SSPE, all of whom, during infancy, developed measles during an outbreak caused by virus of genotype D6 in 1998 [13].

The data in this study suggest a risk of developing SSPE that is ~10 times higher than the risk of developing SSPE estimated in 1982. The risk calculated using the number of cases of measles reported during 1989–1991 may better reflect the true risk of SSPE and may explain the high incidence of SSPE reported in such countries as India, Turkey, and Papua New Guinea [43, 44, 55], where the incidence of measles in very young children is high. The increased risk of developing SSPE after measles virus infection in young children underscores the importance of childhood immunization programs that decrease measles virus transmission and, therefore, reduce the risk of exposure to measles among infants. The success of global programs to eliminate measles will not only prevent the severe complications and death associated with acute cases of measles but will also prevent the devastating disease SSPE.

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References

1. Gascon GG. Subacute sclerosing panencephalitis. Semin Pediatr Neurol **1996**; 3:260–9.
2. Garg RJ. Subacute sclerosing panencephalitis. Postgrad Med J **2002**; 78:63–70.
3. Rima BK. The pathogenesis of subacute sclerosing panencephalitis. Rev Med Virol **1994**; 4:81–90.
4. World Health Organization. Update of the nomenclature for describing the genetic characteristics of wild-type measles viruses: new genotypes and reference strains. Wkly Epidemiol Rec **2003**; 78:229–32.
5. Rota PA, Bellini WJ. Update on the global distribution of genotypes of wild type measles viruses. J Infect Dis **2003**; 187(Suppl 1):S270–6.
6. Jin L, Beard S, Hunjan R, Brown DWG, Miller E. Characterization of measles virus strains causing SSPE: a study of 11 cases. J Neurovirol **2002**; 8:335–44.
7. Croxson MC, Anderson NE, Vaughan AA, et al. Subacute measles encephalitis in an immunocompetent adult. J Clin Neurosci **2002**; 9: 600–4.
8. Rota PA, Bloom AE, Vanchiere JA, Bellini WJ. Evolution of the nucleoprotein and matrix genes of wild-type strains of measles viruses isolated from recent epidemics. Virology **1994**; 198:724–30.
9. Forčić D, Baričević M, Zgorelec R, et al. Detection and characterization of measles virus strains in cases of subacute sclerosing panencephalitis in Croatia. Virus Res **2004**; 99:51–6.
10. Chung BHY, Ip PPK, Wong VCN, Lo JYC, Harding B. Acute fulminant subacute sclerosing panencephalitis with absent measles and PCR studies in cerebrospinal fluid. Pediatr Neurol **2004**; 31:222–4.
11. Ayata M, Kimoto T, Hayashi K, Seto T, Murata R, Ogura H. Nucleotide sequences of the matrix protein gene of subacute sclerosing panencephalitis viruses compared with local contemporary isolates from patients with acute measles. Virus Res **1998**; 54:107–15.
12. Miki K, Komase K, Mgone CS, et al. Molecular analysis of measles virus genome derived from SSPE and acute measles patients in Papua, New Guinea. J Med Virol **2002**; 68:105–12.
13. Barrero PR, Grippo J, Viegas M, Mistchenko AS. Wild-type measles virus in brain tissue of children with subacute sclerosing panencephalitis, Argentina. Emerg Infect Dis **2003**; 9:1333–6.
14. Halsey NA, Modlin JF, Jabbour JT, Dubey L, Eddins DL, Ludwig DD. Risk factors in subacute sclerosing panencephalitis: a case-control study. Am J Epidemiol **1980**; 111:415–24.
15. Zilber N, Rannon L, Alter M, Kahana E. Measles, measles vaccination, and risk of subacute sclerosing panencephalitis (SSPE). Neurology **1983**; 33:1558–64.
16. Subacute sclerosing panencephalitis surveillance—United States. MMWR Morb Mortal Wkly Rep **1982**; 31:585–8.
17. Modlin JF, Jabbour JT, Witte JJ, Halsey NA. Epidemiologic studies of measles, measles vaccine, and subacute sclerosing panencephalitis. Pediatrics **1977**; 59:505–12.
18. Jabbour JT, Duenas DA, Sever JL, Krebs HM, Horta-Barbosa L. Epidemiology of subacute sclerosing panencephalitis (SSPE): a report of the SSPE registry. JAMA **1972**; 220:959–62.
19. Dyken PR. Neuroprogressive disease of post-infectious origin: a review of a resurging subacute sclerosing panencephalitis (SSPE). Ment Retard Dev Disabil Res Rev **2001**; 7:217–25.
20. Gindler JS, Atkinson WL, Markowitz LE, Hutchins SS. Epidemiology of measles in the United States in 1989 and 1990. Pediatr Infect Dis J **1992**; 11:841–6.
21. Orenstein WA, Papania MJ, Wharton ME. Measles elimination in the United States. J Infect Dis **2004**; 189(Suppl 1):S1–3.
22. Hinman AR, Orenstein WA, Papania MJ. Evolution of measles elimination strategies in the United States. J Infect Dis **2004**; 189(Suppl 1): S17–22.
23. Rota PA, Rota JS, Redd SB, Papania MJ, Bellini WJ. Genetic analysis of measles viruses isolated in the United States between 1989 and 2001: absence of an endemic genotype since 1994. J Infect Dis **2004**; 189(Suppl 1):S160–4.
24. Katz SL, Hinman AR. Summary and conclusions: measles elimination meeting, 16–17 March 2000. J Infect Dis **2004**; 189(Suppl 1):S43–7.
25. Zaki SR, Bellini WJ. Measles. In: Connor DH, Chandler FW, Schwartz DA, Manz HJ, Lack EE, eds. Pathology of infectious diseases. Stamford, CT: Appleton & Lange, **1997**:233–44.
26. Koopmans M, Monroe SS, Coffield LM, Zaki SR. Optimization of extraction and PCR amplification of RNA extracts from paraffin-embedded tissue in different fixatives. J Virol Methods **1993**; 43:189–204.
27. Chomczynski P, Sacchi N. Single-step method of RNA isolation by acid guanidinium thiocyanate-phenol-chloroform extraction. Anal Biochem **1987**; 162:156–69.
28. Katz RS, Premenko-Lanier M, McChesney MB, Rota PA, Bellini WJ. Detection of measles virus RNA in whole blood stored on filter paper. J Med Virol **2002**; 67:596–602.
29. Devereaux J, Haeberli P, Smithies O. A comprehensive set of sequence analysis programs for the VAX. Nucleic Acids Res **1984**; 12:387–95.
30. Swofford DL. PAUP: phylogenetic analysis using parsimony. Version 3.1.1. Champaign, IL: Illinois Natural History Survey, **1991**.
31. Dlugos DJ, Brooks-Kayal AR. A 4-year-old with pica, progressive incoordination, and decreased responsiveness. Semin Pediatr Neurol **1999**; 6:164–7.
32. Park SY, Kohl S. Subacute sclerosing panencephalitis in an identical twin. Pediatrics **1999**; 104:1390–4.
33. Honarmand S, Glaser CA, Chow E, et al. Subacute sclerosing panencephalitis in the differential diagnosis of encephalitis. Neurology **2004**; 63:1489–93.
34. Baram TZ, Gonzalez-Gomez I, Xie Z-D, et al. Subacute sclerosing panencephalitis in an infant: diagnostic role of viral genome analysis. Ann Neurol **1994**; 36:103–8.
35. PeBenito R, Naqvi SH, Arca MM, Schubert R. Fulminating subacute sclerosing panencephalitis: case report and literature review. Clin Pediatr (Phila) **1997**; 36:149–54.
36. Koppel BS, Poon TP, Khandji A, Pavlakis SG, Pedley TA. Subacute sclerosing panencephalitis and acquired immunodeficiency syndrome: role of electroencephalography and magnetic resonance imaging. J Neuroimaging **1996**; 6(2):122–5.
37. Nakayama T, Fujino M, Yoshida N. Molecular epidemiology of measles virus in Japan. Pediatr Int **2004**; 46:214–23.
38. Rima BK, Earle JAP, Yeo RP, et al. Temporal and geographical distribution of measles virus genotypes. J Gen Virol **1995**; 76:1173–80.
39. Tipples GA, Gray M, Garbutt M, Rota PA, the Canadian Measles Surveillance Program. Genotyping of measles virus in Canada: 1979–2002. J Infect Dis **2004**; 189(Suppl 1):S171–6.
40. Hutchins S, Markowitz L, Atkinson W, Swint E, Hadler S. Measles outbreaks in the United States, 1987 through 1990. Pediatr Infect Dis J **1996**; 15:31–8.
41. Atkinson WL, Hadler SC, Redd SB, Orenstein WA. Measles surveillance—United States, 1991. MMWR CDC Surveill Summ **1992**; 41(6): 1–12.
42. Miller C, Farrington CP, Harbert K. The epidemiology of subacute sclerosing panencephalitis in England and Wales 1970–1989. Int J Epidemiol **1992**; 21:998–1006.
43. Yalaz K, Anlar B, Renda Y, Aysun S, Topcu M, Ozdirim E. Subacute sclerosing panencephalitis in Turkey: epidemiologic features. J Trop Pediatr **1988**; 34:301–5.
44. Saha V, John TJ, Mukundan P, et al. High incidence of subacute sclerosing panencephalitis in South India. Epidemiol Infect **1990**; 104:151–6.
45. Miller C, Andrews N, Rush M, Munro H, Jin L, Miller E. The epidemiology of subacute sclerosing panencephalitis in England and Wales 1990–2002. Arch Dis Child **2004**; 89:1145–8.

46. Harpaz R. Completeness of measles cases reporting: review of estimates for the United States. J Infect Dis **2004**; 189(Suppl 1):S185–90.
47. Ewert DP, Frederick PD, Run GHF, Mascola L. The reporting efficiency of measles by hospitals in Los Angeles County, 1986 and 1989. Am J Public Health **1994**; 84:868–9.
48. Ewert DP, Westman S, Frederick PD, Waterman SH. Measles reporting completeness during a community-wide epidemic in inner-city Los Angeles. Public Health Rep **1995**; 110:161–5.
49. Miller C, Farrington CP, Harbert K. The epidemiology of subacute sclerosing panencephalitis in England and Wales 1970–1989. Int J Epidemiol **1992**; 21:998–1006.
50. Centers for Disease Control and Prevention (CDC). Measles surveillance report no. 10 1973–1976. Atlanta: CDC, July **1977**.
51. Jabbour JT, Duenas DA, Sever JL, Krebs HM, Horta-Barbosa L. Epidemiology of subacute sclerosing panencephalitis (SSPE): a report of the SSPE registry. JAMA **1972**; 220:959–62.
52. Frings M, Blaeser I, Kastrup O. Adult-onset subacute sclerosing panencephalitis presenting as a degenerative dementia syndrome. J Neurol **2002**; 249:942–3.
53. Singer C, Lang AE, Suchowersky O. Adult-onset subacute sclerosing panencephalitis: case reports and review of the literature. Mov Disord **1997**; 12:342–53.
54. Centers for Disease Control and Prevention. Measles—United States, 1990. MMWR Morb Mortal Wkly Rep **1991**; 40(22):369–72.
55. Takasu T, Mgone JM, Mgone CS, et al. A continuing high incidence of subacute sclerosing panencephalitis (SSPE) in the Eastern Highlands of Papua New Guinea. Epidemiol Infect **2003**; 131:887–98.