Subacute Sclerosing Panencephalitis

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Subacute sclerosing panencephalitis (SSPE) is a progressive neurologic disorder caused by measles virus that silently develops for several years after the primary measles virus infection and is inevitably fatal. The average latency period following primary infection is 6–10 years but can range from 2 to >30 years, and the time from early symptom onset to death is approximately 1–3 years. Though SSPE is the result of a persistent measles virus infection of neuronal and glial cells, much is unknown about the causes of SSPE and no specific immune deficiency has been identified. Early signs and symptoms that precede diagnosis, often confounding clinicians and parents, may include visual impairments, mental deterioration, behavioral changes, and weakness or impairment of motor function, such as difficulties in gait and frequent falls. Although clinical presentations can vary, severe neurologic symptoms such as monoclonic jerks, ataxia, tremors, and seizures are typical among patients with SSPE. Diagnosis is often delayed due to the initial nonspecific sequelae, and is based on clinical presentation and laboratory testing for detection of intrathecal production of antimeasles immunoglobulin G (IgG) antibody or measles RNA in brain tissue. If measles viral RNA is detected, sequence analysis is performed to identify the measles virus genotype, potentially providing insights into when and where the primary measles virus infection was likely to have occurred years earlier. Several studies that analyzed measles sequences from SSPE cases concluded that the live attenuated vaccine strains do not cause SSPE [1, 2]. The marked decline of SSPE, concurrent with the decline in measles after the introduction and widespread use of measles vaccine, demonstrates that the vaccine protects against SSPE.

The risk of developing SSPE cited in the older literature was 1–8.5 cases per 100,000 cases of measles [3]. In the early to mid-1970s, the risk for developing SSPE was calculated at a time when measles was endemic, and the denominator was based on a crude estimate for the annual number of measles cases [4]. Although an SSPE registry was established in the United States in 1969 [5], the completeness of the register was unknown, and it is likely that underdiagnosis of SSPE contributed to the lower estimates of risk for SSPE.

The results of more recent studies make it apparent that the burden of SSPE as a cause of measles morbidity and mortality has been underappreciated. The article by Wendorf et al in this issue of Clinical Infectious Diseases is the second published study focusing on the risk of developing SSPE following the resurgence of measles in the United States from 1989 to 1991. These studies gave a more accurate estimate of the risk of developing SSPE because the authors could study SSPE cases occurring after measles elimination following a nationwide outbreak with >50,000 cases. These investigations were facilitated by the implementation of improved surveillance that provided more accurate measurements of the annual number of measles cases. The availability of newer laboratory methods provided a greater range of diagnostic options, and sequence data were often able to indicate the source of the initial measles virus infection.

Wendorf et al reported on SSPE cases detected in California, and estimated the risk of SSPE for children who contracted measles at <5 years of age and infants <12 months of age to be 1:1367 and 1:609, respectively. A report by Bellini et al [1] that analyzed all available data for SSPE cases in the United States that had measles during the resurgence, irrespective of the age of primary infection, estimated the risk to be approximately 1:5000 (preliminary estimate; the final estimate was adjusted to reflect a 30%–50% underreporting of cases during the resurgence). Risk estimates based on investigations in the United Kingdom were approximately 1:25,000 overall and 1:5500 when measles occurred during the first year of life [6–8]. A German study also focused on younger age groups and estimated the risk to be approximately 1:700–1:3300 [9].

In any setting, the calculation of an accurate risk estimate for SSPE is
exceedingly difficult. For the denominator, completeness of measles case reporting relies on patients seeking healthcare and measles case confirmation by laboratory testing or by epidemiologic linkage. It is well documented that the number of reported cases represents only a portion of all measles cases. Reporting efficiency of measles cases is context-specific, and can be appreciably higher for hospitalized cases than those diagnosed in an outpatient setting and during outbreaks. Publicity surrounding measles when outbreaks occur may increase recognition and accurate diagnosis, although a study in the United States that compared completeness of reporting in a nonepidemic year compared to 1989, the first year of the resurgence, showed that the proportion of cases identified from patient records that were reported to health departments did not increase [10]. Furthermore, adequate epidemiologic information (ie, evidence that the primary measles virus infection occurred during the study time period and geographic location) is difficult to obtain. Many measles virus infections are often unrecognized in infants if signs and symptoms are milder due to the presence of maternal antibodies. Therefore, it might be particularly difficult to assign an accurate denominator of measles cases for infants <12 months of age.

SSPE is not a reportable disease, and surveillance systems are not established to detect and report SSPE cases. Because early SSPE signs and symptoms are non-specific and have a delayed onset, usually years after the initial measles virus infection, SSPE cases largely go undiagnosed, particularly in resource-limited settings. In the developing world, the capacity of health systems to provide diagnostic testing to differentiate neurological complications is severely limited. A measles death is defined as a confirmed measles case in which death occurs within 30 days of rash onset, without another unrelated cause; therefore, the deaths from SSPE are not included in global mortality estimates [11, 12], so the global burden of SSPE is unknown. However, by applying a conservative risk of 1:4000 to the estimated number of surviving measles cases in 2015 (9,451,200), approximately 2400 SSPE cases would not have been accounted for in mortality estimates.

SSPE incidence depends on the measles epidemiology of a particular setting, in part because the risk for SSPE is higher when the primary measles virus infection occurs at a younger age. A consistent finding in SSPE investigations is that the risk of developing SSPE is higher when measles is contracted at <5 years of age. Measles virus infection at <12–15 months of age carries an even higher risk. As the risk of developing SSPE is highest when primary measles virus infection occurs before 12 months of age, it is imperative that vaccination programs achieve high coverage to provide the herd immunity needed to protect infants too young to be eligible for vaccine.

As discussed above, there are many caveats associated with estimating the risk of SSPE. However, based on the recent efforts described above, including the report by Wendorf et al, it appears that the previous estimates were too conservative and that characterization of SSPE as being a rare complication of measles should be reconsidered. Therefore, in addition to the prevention of complications including fatal outcomes that can result from acute measles, prevention of SSPE might be considered as an advocacy tool to help global vaccination programs achieve the high vaccination coverage needed to protect vulnerable infants. Furthermore, recommendations for the administration of measles vaccine as early as 6 months of age should be followed to prevent measles and complications in settings or outbreaks in which infants are at high risk for exposure to measles virus [13].

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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