A Re-emergence of Subacute Sclerosing Panencephalitis in the United Kingdom

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Abstract: New pediatric and adult subacute sclerosing panencephalitis cases between 1996 and 2020 were reported based on an established UK registry with no evidence of under-ascertainment using a separate pediatric surveillance system. After 15 years with no pediatric UK-acquired cases, 3 cases arose from 2017 after increased modeling. Modeling suggested this was in line with measles notifications, underreporting of laboratory-confirmed measles or increased subacute sclerosing panencephalitis risk.

Keywords: subacute sclerosing panencephalitis, measles, vaccination, measles-mumps-rubella, surveillance

SUBACUTE SCLEROSING PANENCEPHALITIS AND MEASLES

Subacute sclerosing panencephalitis (SSPE) is a rare but fatal late neurologic complication of measles. Symptoms start on average 4–10 years after primary childhood measles with a slow progressive encephalitis, although much longer latency can occur. Between 2016 and 2019, there was a measles epidemic affecting European Union/European Economic Area Member States interrupted by coronavirus disease 2019 (COVID-19) pandemic–associated control measures. Highest rates were reported in infants, increasing the risk for new SSPE cases.

This study reports on UK SSPE epidemiology from 1996 to 2020 based on new child and adult cases reported to the national SSPE registry, and models expected pediatric cases using measles surveillance data from 2 sources. We used data from a separate pediatric surveillance system to determine any under-ascertainment in the SSPE registry.

Incidence has been estimated at 4–11 SSPE cases per 100,000 measles cases but occurs at a higher rate (circa 1:5555) after infant disease,2 more recently estimated as 1:3000 after disease <5 years and as high as 1:609 after infant measles.4,5 UK measles vaccination was introduced in 1968 with initial low uptake increasing through the 1980s and, boosted by the 1988 introduction of measles-mumps-rubella (MMR) vaccine, exceeding 90% from 1992. As in other countries, measles activity declined dramatically with high vaccine coverage with a resultant marked fall in UK SSPE, from an average 18.1 cases (0.03 per 100,000 population) to 9 (0.02 per 100,000) and 5 (0.01 per 100,000) reported annually in the 1970s, 1980s, and 1990s respectively, with no UK-acquired cases by the early 2000s.

MMR uptake fell in the early 2000s to 79.9% at 24 months of age in 2003/2004, after the now discredited postulated link between the vaccine and autism, and measles cases increased from the mid-2000s. With improved MMR coverage, exceeding 90% from 2011/2012, and targeted campaigns to capture teenagers with low coverage, measles cases declined, and the United Kingdom achieved World Health Organization (WHO) measles elimination status in 2016. However, routine vaccine uptake gradually declined again from 2013 and cases re-emerged. In 2019, the WHO classified measles outbreaks across Europe as a Grade 2 emergency, and the Regional Verification Committee of the European WHO Region for Measles and Rubella Elimination concluded that the United Kingdom, Albania, the Czech Republic and Greece had lost their measles elimination status.6,7 The COVID-19 pandemic put further pressures on routine vaccine delivery with falls in coverage. While measles cases were low during pandemic control measures, global increases are being seen with their withdrawal.

UK SSPE REPORTING

The UK SSPE registry, currently managed by the UK Health security Agency (UKHSA), was established in 1970. Cases were ascertained through reports to the UK SSPE registry with confirmatory testing at the National Measles Laboratory, UKHSA Viral Reference Department or as diagnostic testing with samples sent directly to the UKHSA Viral Reference Department. Laboratory diagnosis was by detection of very high viral index or detection of mutated measles virus RNA in brain tissue. Death certificates were also routinely reviewed for measles-related deaths, with no additional SSPE cases identified for the period observed.

Data were collected by the UKHSA SSPE Registry team on clinical features, investigations, vaccination history and measles disease history with annual follow-up with the lead clinician for each registered case. Initially, only cases with UK-acquired measles were followed up. Since 2000, all SSPE cases underwent surveillance with only those considered UK-acquired included in UK figures. We describe the epidemiology of UK SSPE cases with onset between 1996 and 2019.

To examine whether there was any under-ascertainment of pediatric cases, we used a separate data source to undertake
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a capture-recapture analysis. The UK-wide study of progressive intellectual and neurological deterioration (PIND) in children was established in 1997 and uses the British Pediatric Surveillance Unit active surveillance system to identify children <16 years of age with PIND. All UK consultant pediatricians are prompted to report new cases of PIND seen in the previous month.9

RECENT SSPE EPIDEMIOLOGY

After low levels of measles activity during the 1990s, no cases of SSPE after UK-acquired measles in children <16 years of age were identified for 15 years between 2002 and 2016. In this period, there was one confirmed adult SSPE case with symptom onset in 2009.

Between 2017 and 2019, however, 6 cases of pediatric SSPE were reported (described clinically in Lam et al10). Two cases had UK-acquired measles, 3 were infected abroad and 1 with no known travel or measles symptoms is a presumed UK-acquired case.

Symptom onset in the 2 cases with UK-acquired measles was at 4 and 6 years of age after measles disease at <1 year and 2 years of age, respectively. One acquired measles during 2013, before vaccination, and the other unvaccinated child was infected in 2016. Latency between measles infection and SSPE symptom onset was 2.5 and 4 years. This compares with a mean latency of 10 years (range 4–15 years) in 10 SSPE cases <16 years of age with measles dates available and onset between 1996 and 2003.

Between May 1997 and December 2019, 8 pediatric SSPE cases with UK-acquired measles were notified to the PIND Study and were eligible for, and independently reported to, the UK SSPE register providing reassurance that cases were not missed. Nineteen SSPE cases were reported to the SSPE register that were not captured through the PIND Study; 3 developed diseases in 1996 before the PIND Study commenced, and a further 12 were ≥15 years of age at symptom onset (range 15–29 years) and would not have been reported to the PIND Study unless diagnosed under pediatric care.

Using a model (incorporating age-specific SSPE risk and latency distribution) previously described,11 the expected number of cases in England and Wales 1990–2019 was calculated (no SSPE cases arose in Scotland or Northern Ireland). Two scenarios were assessed to determine the observed and modeled cases (Fig. 1), 1 with incidence since 1996 using measles notification data (reported on clinical judgment without requiring laboratory confirmation) and 1 using laboratory-confirmed cases. Using notified and laboratory-confirmed data, the expected SSPE case numbers between 2015 and 2019 were 1.26 and 0.33 cases, respectively. The observed number of 3 cases was consistent with expected cases using notifications (P = 0.13 of observing 3 or more when expected = 1.26) but was higher than expected based on confirmed cases (P = 0.005 of observing 3 or more when expected = 0.33).

DISCUSSION

National UK SSPE surveillance appears to be robust with no unreported cases identified through independent pediatric surveillance of neurological deterioration. After 15 years with no pediatric cases, SSPE re-emerged in the United Kingdom after measles cases increased between 2006 and 2013. Two cases followed known UK-acquired measles with one presumed to be

FIGURE 1. Observed and expected SSPE cases after measles acquired in England and Wales only based on laboratory confirmed and notified measles (England and Wales), 1990–2019.
UK-acquired. Modeling found observed SSPE cases were consistent with measles notifications but higher than expected based on laboratory-confirmed cases (\(P = 0.005\)) suggesting actual measles cases were much higher than those laboratory-confirmed or, if correct, that the cluster of 3 SSPE cases indicated an increased risk per measles case.

The 3 cases were born in 2012 and were infected young with early SSPE onset and a correspondingly short latency. The range of SSPE latency length means we may yet see cases in older children with longer latency who were also infected during the 2012/2013 measles peaks when 77% (8044/10,404) of notifications in England and Wales were <5 years and 19% (2014/10,404) were infants.

The UK case without documented measles likely acquired infection in 2012/2013, before vaccination, during increased disease in the local area making it probable that all 3 UK-acquired cases were infected with a D8 genotype, which dominated in 2012–2013 and 2016. In other higher measles years, the dominant genotype was either B3 or D4. Although association of different genotypes with SSPE has not been extensively studied, low incidence of SSPE in Africa has been explained by decreased association of the B3 measles genotype with SSPE.

The elimination of measles was short-lived, and activity increased again in the 2 years preceding the SARS-CoV-2 pandemic, both globally and within the United Kingdom and other European countries, which may result in further cases of SSPE. As we emerge from COVID-19 control measures, clinicians should consider SSPE among the differentials in a child presenting with progressive neurologic, behavioral or intellectual deterioration.

Vaccination protects against SSPE by preventing measles, with the potential to eliminate SSPE. Maintaining 95% vaccination coverage or higher for both MMR vaccine doses helps prevent infant measles through herd protection. Timely routine vaccination offers optimal direct protection according to national schedules. The risk of younger infants acquiring measles abroad associated with travel to high endemic areas or those with measles outbreaks can be minimized by following national guidance; 1 UK SSPE case had travel-associated measles at 8 months of age.

**CONCLUSION**

This review of UK SSPE cases from 2 national surveillance systems provides reassurance that cases are not being missed, although confirmatory testing of measles is underutilized. Pediatric SSPE had disappeared for 15 years, and its re-emergence is a stark reminder that measles is not a mild disease. This review of UK SSPE cases from two national surveillance systems provides reassurance that cases are not being missed, although confirmatory testing of measles is underutilized. Paediatric SSPE had disappeared for 15 years and its re-emergence is a stark reminder that measles is not a mild disease. To prevent further SSPE cases, timely and sustained uptake of measles-containing vaccine at ≥95% is essential, requiring reversal of recent declines in coverage.

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