

## **A recent surge of fulminant and early onset subacute sclerosing panencephalitis (SSPE) in the United Kingdom: An emergence in a time of measles**

### **Names and affiliations of all authors:**

Dr Tanya Lam, MD, MPH, DTMH, Children's Neuroscience Centre, Evelina London Children's Hospital, Guy's and St Thomas' NHS Trust, London, U.K. Great Ormond Street Hospital for Children, London, U.K.

Dr Rajesh Ranjan, MD, MRCPCH, Paediatric Neurology, Noah's Ark Children's Hospital for Wales, Cardiff, U.K.

Dr Kerensa Newark, MBBS, Paediatric Neuroscience Department, Leeds Teaching Hospitals NHS Foundation Trust, Leeds, U.K.

Dr Snehal Surana, MBBS, MD, MRCPCH, Paediatric Neurology, Great Ormond Street Hospital for Children, London, U.K.

Dr Neeraj Bhangu, MBBS, MRCPCH, Paediatric Neurology, Southampton Children's Hospital, Southampton, U.K.

Dr Abigail Lazenbury, MBBS, Paediatric Neurology, Southampton Children's Hospital, Southampton, U.K.

Dr Anne-Marie Childs, MBBS, MBChB, MRCP, FRCPCH, Paediatric Neuroscience Department, Leeds Teaching Hospitals NHS Foundation Trust, Leeds, U.K.

Dr Ianthe Abbey, MBBS, MRCPCH, MMedSci, General Paediatrics, York Teaching Hospital NHS Foundation Trust, York, U.K.

Dr Frances Gibbon, MBBS, FRCPCH, Paediatric Neurology, Noah's Ark Children's Hospital for Wales, Cardiff, U.K.

Dr Gareth Thomas, MBBS, FRCPCH, Paediatric Neurology, Morriston Hospital, Swansea, U.K.

Dr Jaspal Singh, MBBS, FRCPCH, Paediatric Neurology, Southampton Children's Hospital, Southampton, U.K.

Dr Prab Prabhakar, MBBS, FRCPCH, Paediatric Neurology, Great Ormond Street Hospital & UCL-GOSICH, London, U.K.

Dr Margaret Kaminska, MD, Children's Neuroscience Centre, Evelina London Children's Hospital, Guy's and St Thomas' NHS Trust, London, U.K.

Dr Karine Lascelles, MD, Children's Neuroscience Centre, Evelina London Children's Hospital, Guy's and St Thomas' NHS Trust, London, U.K.

Dr Yael Hacohen, MD, PHD, Queen Square MS Centre, UCL Institute of Neurology, Faculty of Brain Sciences, University College London. Department of Paediatric Neurology, Great Ormond Street Hospital for Children, London, U.K.

Dr Kevin Brown, MD, MRCP, FRCPath, Consultant Medical Virologist, Virus Reference Department and Immunisation and Countermeasures Division, Public Health England, U.K.

Dr Ming Lim, MD, PHD, Children's Neuroscience Centre, Evelina London Children's Hospital, Guy's and St Thomas' NHS Trust, London, U.K. Faculty of Life Sciences, King's College, London, U.K.

**Co-corresponding authors:** Dr Tanya Lam tanya.lam@nhs.net; Dr Ming Lim ming.lim@gstt.nhs.uk

### **Highlights:**

- **SSPE is a lethal neurodegenerative condition that follows measles infections, it has been very rare in the UK in the last two decades.**
- **We present the most significant UK cohort in the last 20 years, supporting rates described in the US and Germany.**
- **Acute fulminant disease occurred in all cases rather than being a rare trajectory and the majority of cases presented with atypical symptoms and investigations, making diagnosis challenging. Cases were younger than previously described cohorts, with short latency periods.**
- **The majority of cases were fully vaccinated, but had exposure during infancy, between 6-12 months before the scheduled MMR dose.**

# **Abstract**

## **Background**

Subacute Sclerosing Panencephalitis (SSPE) is a devastating and fatal illness following measles infection. Since the introduction of the measles vaccine in 1968, SSPE rates dropped significantly in the United Kingdom (UK) to five cases over the 15 years through to 2016.

## **Methods:**

Cases of clinical and laboratory confirmed SSPE were collated from Paediatric Neurology centres in the UK over a 22-month period from 2017 to 2019 and represent all known cases referred to the National Viral Reference Department (VRD). Diagnosis was established according to the national standard, with detection of a raised measles index in all cases, demonstrating intrathecal measles antibody production.

## **Findings:**

Over this 22-month period (2017- 2019), six children presented with acute fulminant subacute sclerosing panencephalitis. The majority were vaccinated, but had acquired measles in infancy prior to immunisation. Presentations were heterogenous and required repeat investigations to establish diagnosis. The cases presented at an earlier age (median 5 years, range 2-7 years), with short latency (median 3, range 2-6years) and all progressed to fulminant SSPE within six months of diagnosis.

## **Interpretation:**

Six cases in 22 months represents the highest number of SSPE cases seen in the UK in since 2000. All cases were acute fulminant disease, occurring at younger ages highlighting the importance of clinician awareness of SSPE as a differential diagnosis in

any child presenting with neurological regression. Health care providers, educators and governments need to ensure resources continue to target effective education and access to immunisation programmes, the only means to combat this untreatable and fatal condition.

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**Supplemental data:** *Detailed case description; 1 table; 3 figures*

## **A recent surge of fulminant and early onset subacute sclerosing panencephalitis (SSPE) in the United Kingdom: An emergence in a time of measles.**

### **Introduction**

Subacute sclerosing panencephalitis (SSPE) is a progressive and fatal central nervous system disease occurring following reactivation of the measles virus. SSPE is named in reflection of its predominantly subacute course and is described in stages I to IV, taking between one to four years to progress through the stages (Supplemental Table 1),<sup>2</sup> though a large cohort in Japan demonstrated a mean survival of nine years (range 2-21).<sup>3</sup> Acute fulminant and slow fluctuating courses occur in 5-10% of cases, defined by moderate disability by three months of onset, and or death or severe disability by six months from onset.<sup>4</sup> Prolonged remission occurs in 5% of cases and adults more frequently have slower progression.<sup>5</sup> Death is usually from respiratory-bulbar dysfunction or infection and usually occurs in stage IV but can occur at any stage.<sup>6</sup>

Calculating the incidence of SSPE following measles infection is reliant on robust data on both conditions. Reported and notified cases are a fraction of the true number of measles cases. The last two years has seen a tripling of reported measles cases in Europe, 2019 brought the highest number of cases seen in the US since elimination in 2000, and globally over half a million cases were reported.<sup>7,8</sup> Measles outbreaks are followed by increased SSPE cases downstream, with SSPE occurring 5-20 times more frequently during outbreaks than during well controlled periods, assuming a latency of seven years.<sup>9</sup>

From the national 1970s registry data, SSPE was estimated to occur in 1 in 25,000 measles infections, with a higher rate of 1 in 5500 following infections during infancy.<sup>10</sup> Recent cohorts have suggested higher incidence rates. In California, adjusting for a

measles reporting rate of 50%, SSPE occurred in 1 in 2700 of those contracting measles between 1-5 years of age and in 1 in 1200 of those contracting measles during infancy.<sup>11,12</sup> A German study of cases through to 2009 found rates of SSPE between 1:1700 to 1:3300 in those exposed to measles before the age of five. The range of incidence varied depending on whether cases with foreign birth or foreign exposure to measles were included.<sup>13</sup>

We present six recent cases of SSPE that presented in the UK over a 22-month period from May 2017 to Feb 2019, signalling a potential emergence of SSPE prior to the recent surge of measles. All cases were of the acute fulminant subtype and occurred in younger children, with short latency periods.

### **Methods**

Cases of clinical and laboratory confirmed SSPE were identified in conjunction with National Viral Reference Department (VRD, PHE) in five Paediatric Neurology centres in the UK over a 22-month period from 2017 to 2019. Diagnosis was established per the national standard, with detection of a raised measles index in CSF and serum, demonstrating intrathecal production, performed at the National Viral Reference Department (VRD).

### **Results**

A total of six patients were identified (five male), presenting at a median age of five years (range 2-7years) and median latency period of three years (range 2-6 years). Five of the vaccinated children had were suspected to have acquired measles prior to vaccination, four with a history of erythematous rash and fever in infancy. The sixth child was an unvaccinated 3-year-old who contracted measles from his unvaccinated older sibling. Measles exposure had been in the UK for at least three children. One in

whom there was no clear exposure to measles and had never left the UK (Case 3). In case 6 an infant presented shortly after return from vacation in Pakistan, and was diagnosed as a non-specific viral illness. The detailed clinical history of each of the cases is provided in the supplemental data whilst the key clinical and investigative features and disease course is summarised in Table 1. Classification and staging of disease is described in Supplemental Table 1.

#### *Clinical Presentation and Disease Progression*

Before the onset of SSPE, all children were well and developmentally age appropriate and none were found to be immunocompromised. Initial symptoms were often non-specific, subtle and in some only retrospectively identified. These symptoms presented between two weeks to six months prior to first hospital contact, comprising unsteady gait causing falls (Cases 1, 4, 5 and 6); behavioural change (Case 4, and 6); intermittent confusion; visual disturbance (Case 2 and 3); decline in reading and writing ability (Case 2 and 5); poor school performance (all school age cases); headache and vomiting (Case 2) and abdominal pain (Case 3).

As the disease progressed, a more consistent neurological phenotype emerged with cognitive regression, seizures and neurological decline. Seizure types included atonic drops (Cases 2, 4 and 6), focal and generalised seizures (Cases 1, 2 and 3), atypical absences (Case 2), eyelid myoclonia (Case 3) and epilepsy partialis continua with associated hemiplegia (Case 2). The classically described myoclonic jerks of stage II disease were described in five of the cases, but occurred as late as eight months into illness. Dystonia and status dystonicus developed in five of the patients (Cases 1, 3, 4, 5 and 6).

### *Investigative findings*

CSF microscopy, cell count, and biochemistry were unremarkable in all cases. CSF intrathecal bands were present in all cases. CSF measles IgG testing in one case had been negative when tested overseas, however on repeat testing extremely high IgG titres were found (Case 4). IgG titres did not correlate with severity of disease, but all had raised IgG indices compared to the normal level, and raised measles index (>5.0) (Table 1). Whilst PCR is typically negative due to the absence of extracellular viral release,<sup>14</sup> one patient was reported to have had a positive measles PCR, prior to requesting serology (Case 6). Overall, imaging changes at presentation were heterogeneous and discordant to clinical severity. When abnormal, the consistent imaging finding was of asymmetric white matter changes which progressed from subcortical to periventricular regions (Case 1 and 6). Global cerebral atrophy then ensued and was observed as soon three months (Case 4, Supplementary Fig 3) to two years (Case 2).

Characteristic periodic complexes with slow background, during stage II of disease (Supplemental Table 1; also summarised in Table 1) was seen in five patients. However, took up to eight months from onset to appear (Supplemental Fig 1 and 2). The one patient who did not have periodic complexes on EEG, had limited images available for review from overseas investigations (Case 4). Additional SSPE features of frontal dominance high amplitude sharp and slow waves were noted in two cases (Cases 5, 6). One patient with focal seizures had corresponding left sided epileptogenic focus, progressing to EPC (epilepsy partialis continua), before evolving to periodic complexes (Case 2). In five cases, serial EEG demonstrated progression to encephalopathy.

### *Treatment and outcome*

A range of immunomodulatory and or anti-viral strategies were given to four children (Table 1). Three cases received empirical methylprednisolone prior to establishment of diagnosis. Two of these had marked clinical deterioration temporally related to steroid use, there was no clinical status change in the third. The rapid deterioration in all cases fulfilled criteria for acute and fulminant disease (Supplemental Table 1).<sup>4</sup> The patient who was eldest (3yo) at exposure to measles, died within three months of onset.

### **Discussion**

We present a series of six patients with acute and fulminant SSPE, who presented over a 22-month period in the UK. Due to its rarity, particularly in the last 20 years, and the lack of recognised effective treatment, there is no national guidance on SSPE management. Notably, all our cases were fulminant, which is expected to occur in only 5-10% of previously reported cases.<sup>4</sup> All cases were managed with a multidisciplinary approach.

For clinicians, our cases serve as a reminder that SSPE must remain a diagnostic consideration in vaccinated individuals, and should be part of the differential diagnoses for a wide range of neurological presentations. The classical description of SSPE is onset of myoclonic jerks in stage II of disease, with corresponding periodic complexes seen on EEG. The majority of our cases had less typical features, with myoclonic jerks presenting late into disease.

A high level of clinical suspicion and preparedness to repeat investigations is key in establishing diagnosis. Serial EEGs up to eight months following onset were necessary to eventually demonstrate the characteristic EEG findings. Similarly, though diagnostic

confirmation through isolation of Measles IgG on CSF is usually straightforward, in one patient initially investigated abroad, results were negative. Neuroimaging was discordant to clinical findings and remained normal in the setting of both hemiparesis and severe cognitive decline. Discordance, white matter changes and global atrophy are findings consistent with previous cohorts.<sup>15</sup>

The broad constellation of atypical presentations, led to half the cases being treated with methylprednisolone. As corticosteroids may potentiate a decline in clinical condition, this presents a pitfall in empirical management, particularly in settings where SSPE is uncommon and steroid treatments for inflammatory and post-inflammatory conditions will be more familiar.<sup>2,16</sup> All the six cases rapidly progressing to end stage disease, limits the interpretation of the effect of corticosteroid treatment. Although two cases had modest transient improvement, immunomodulation and or anti-viral strategies ultimately provided no gain in neurological outcome, with inexorable progression of disease.

SSPE is a disease that primarily affects children, but has been recorded in infants from four months following perinatal intrauterine infection through to adults up to 56 years.<sup>17,18</sup> Our cohort were younger than other cohorts (median 5 years; age range 2-7 years vs median 9.5-12.5 years).<sup>9,13,18-20</sup> Concurrently the latency period in our cases was shorter (median 3 years; range 2-6years vs median 7years).<sup>9</sup> The male predominance of our cohort is consistent with previous reports (2.4:1 vs range 0.7-7.1:1).<sup>9</sup> Beyond gender, further genetic vulnerability has been postulated, with only a third of Melanesian children developing lasting measles antibodies and the highest rates of SSPE found in Papua New Guinea.<sup>21</sup>

Whilst earlier vaccination from 6 months of age is recommended in settings of outbreak and endemic measles, routine schedules in many countries including the UK provide MMR1 at 12 months. Measles vaccine strains are not associated with SSPE as wild type measles genome has consistently been isolated from brain tissue of SSPE patients and matched to the circulating genotype.<sup>9,11,22</sup> Thus, SSPE in vaccinated patients is attributed to infection prior to immunisation, or rarely vaccine failure.<sup>9,19,23</sup> The majority of our cases were vaccinated according to schedule but had already been exposed and infected with measles during infancy (between 7-9months). A recent systematic review of studies measuring the effectiveness of measles vaccination in infants younger than nine months found high seroconversion and vaccine effectiveness after two doses, with minimal blunting effect on antibody titres.<sup>24</sup> Our single case exposed beyond infancy was unvaccinated. The child died within three months of onset, supporting previous cohort findings that later exposure age to measles was more likely to have a shorter time course to death.<sup>19</sup> Infantile measles exposure prior to protection with scheduled vaccination, combined with the higher rates of progression to SSPE following exposure,<sup>10,12,13</sup> highlights the critical role of herd immunity in protecting infants and other vulnerable groups from infectious diseases.

National SSPE registries have been kept in the United States (US) and the United Kingdom (UK) since the 1970s. Data collected includes those with exposure within the country and internationally, reflecting global travel and migration.<sup>10</sup> The measles vaccine was introduced in 1968 and whilst vaccination rates in the 1970s was less than 70%, over 100,000 cases of measles were seen annually.<sup>19</sup> The decline in measles cases resulting from successful vaccination programs is reflected in the subsequent decline of SSPE cases. SSPE cases in the UK went from 20 per year in the 1970's to approximately six per year in the 1990s. This decline continued, with only five cases diagnosed from 2000 to 2016. Our six cases in under 24months represent an increase in cases

compared to the last 20 years (Figure 1). At least three of our cases were exposed to measles in the UK, compared to only two cases during the 12 years prior (2006-2017).<sup>19</sup> The WHO recommends 95% coverage of MMR2 by five years of age for measles elimination. This level of coverage has never been reached by the UK. Instead, vaccination rates have continued to decrease for the 5<sup>th</sup> consecutive year, despite over 10 000 notified cases in 2012-2013. In 2019 MMR2 coverage was 86.4% nationally and as low as 64.1% in boroughs of London.<sup>25</sup>

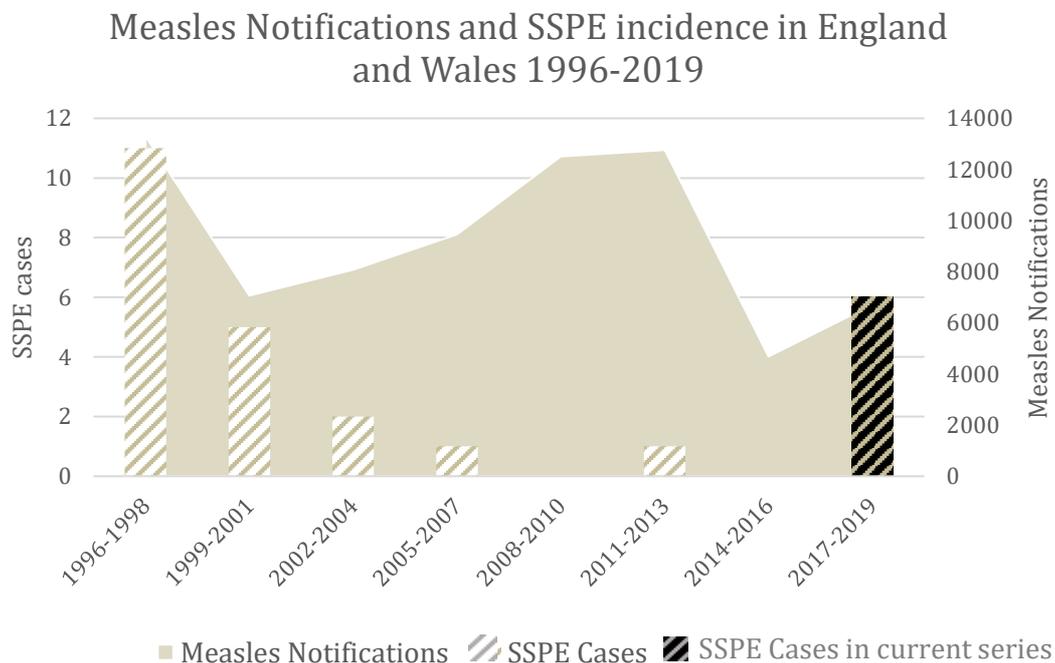


Figure 1. Incidence of measles notifications and SSPE in the UK between 1996 – 2019 in England and Wales. Cases cohort in 2017-2019, at least half had exposure in the UK<sup>1,19,26</sup>

Our series of cases, all with acute fulminant disease, occurring at younger ages, in previously well children and all leading to catastrophic neurological decline calls for the need of more vigilance. Though short latency was seen in our cohort, this varies and both measles and SSPE are recognised as being underreported globally. Continual

reporting via the British Paediatric Surveillance Unit and Public Health England are required to monitor this closely.<sup>2728</sup>

These recent cases provide key public health messages. Firstly, the recent global rise in measles cases should prompt health professionals and governments to anticipate a highly probable increase in rate of SSPE and thus clinicians who mostly likely have never seen a case, need to consider a broad range of presentations as potentially caused by SSPE. Beyond the atypical presentations that are diagnostically challenging, cases may like ours be younger and have more aggressive disease. The predominant infantile measles exposure and recent analysis confirming effectiveness of 6-9month vaccine dosing, raises the question of whether broader earlier scheduling of vaccination would prevent a substantial proportion of SSPE cases. Finally, as the world continues to cope with the SARS-CoV-2 pandemic, it remains the vital responsibility of health care providers, educators and governments to ensure resources continue to target effective education and access to immunisation programmes, the only means to combat this untreatable and fatal condition.

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Case	Age of onset, gender, birth country	History of measles like illness	Exposure location, age	Latency between measles and SSPE	Completed Vaccination Schedule	Presenting Features	Seizures	Movement disorder/ Motor disturbance	MRI	EEG: Periodic complexes noted?	Immunotherapy	Clinical improvement	Outcome and duration of follow up
1	2yo male, Eithiopia	Yes, clinically suspected, known contact	Eithiopia, 9 mo	2 years	Yes	Falls, clumsiness	Generalised, myoclonic	Dystonia	Subcortical white matter lesions involving most of the left parietal lobe	Yes; (1 month, stage II): Periodic complexes, associated with slow head nods	None	N/A	Death, 2.5yrs
2	5yo, female, UK	Yes, recalled symptoms, during local outbreak	UK, 8mo	3 years	Yes	Headache and vomiting, colour vision disturbance	GTC, focal, absences, myoclonic	Hemiparesis, tremor	Normal. F1 (7mo): Normal. F2 (2yrs): Global atrophy with increased signal in fronto-parietal white matter.	Yes; (5 months, stage II): Left sided epileptogenic focus. F1 (7 months, stage II): Persistently firing epileptogenic focus: epilepsy partialis continua. F2 (8 months, stage II): Periodic complexes.	None	N/A	Stage IV, 2 years
3	5yo male, UK	No	UK, Unknown	Unknown	Yes	Abdominal pain, right sided visual disturbance	Nocturnal focal, GTC, Myoclonic	Dystonia, ataxia	Normal. F1(7mo): Normal	Yes; (1 month, stage II): Periodic complexes, spreading from anterior to posterior, with associated eyelid myoclonia.	Oral Rb, IVIG, KD	Initially stage III to II	Stage IV, 2 years
4	5yo male, Pakistan	Yes, clinically suspected	Pakistan, 7mo	5 years	Yes	Behavioral disturbance, falls	Myoclonic	Dystonia	Normal. F1 (5mo): Global atrophy with diffusely increased signal in the white matter.	No; (3 months, stage II): Periodic bursts of polyspike and wave activity, attenuated background. F1 (5months, stage III): Encephalopathic	IVMP, INO, IVIG	Minimal	Stage III, 2 years
5	6yo male, UK	Yes, clinically suspected, sibling confirmed	UK, 3 years	3 years	No	Falls, tiredness, altered handwriting and speech	Myoclonic	Dystonia, ataxia	Normal. F1 (2mo): Normal	Yes; (1 month, stage II): Periodic complexes, with bifrontal prominence. F1 (2months, stage III): Encephalopathic.	IVMP, INO, IVIG	No	Death, 3months
6	7yo male, UK	Yes, recalled symptoms	UK/ Pakistan, 9 mo	6 years	Yes	Behavioral disturbance, falls	Atonic drops	Dystonia	Asymmetrical signal change in subcortical and deep white matter. F1 (7mo): Bilateral periventricular white matter changes.	Yes; (6 months, stage II): Frontal dominance of continuous high amplitude sharp and slow wave activity. F1 (6 months, stage II): Diffusely slow background with periodic frontal sharp waves. F2(8 months, stage II): Periodic complexes.	IVMP, IVIG	No	Stage III, 18 months

Table 1. Cases of SSPE in the UK 2017-2019. Key: F= Follow up, IVIG= Intravenous Immunoglobulin, IVMP = Intravenous methylprednisolone, INO= Inosiplex, KD= Ketogenic Diet, Rb = Ribavirin