CLINICAL ALERT

Subacute sclerosing panencephalitis in South African children following the measles outbreak between 2009 and 2011

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Edward Kija completed his training in the Paediatric Neurology Unit, Department of Paediatrics and Child Health, Red Cross War Memorial Children’s Hospital (RCWMCH) and the Faculty of Health Sciences, University of Cape Town, South Africa, where he collated the patient data included in this study. He has since returned to work as the first accredited paediatric neurologist in Dar es Salaam, Tanzania. Alvin Ndondo, a consultant in the Paediatric Neurology Unit, was integral in the clinical recognition and diagnosis of these children. Graeme Spittal, a paediatrician in the Paediatric Neurology Unit, assisted in their management. Diana Hardie works in the Division of Medical Virology in the Department of Clinical Laboratory Sciences, Faculty of Health Sciences, University of Cape Town and National Health Laboratory Service. She completed in the collation of the data on the patients and relevant aspects in the literature. Jo Wilmshurst is head of paediatric neurology at RCWMCH and the Faculty of Health Sciences, University of Cape Town. She co-managed the patients, oversaw the data collation and co-ordinated the writing of the manuscript.

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Between 2009 and 2011, there was an outbreak of measles throughout South Africa (SA). The largest age category infected was children <5 years of age. In 2014, four patients, with a median age of 4 years and 5 months (range 4 years 3 months - 4.5 years), three males and one female, presented with subacute sclerosing panencephalitis (SSPE). All were infected with measles during the period of the 2009 - 2011 outbreak in early infancy, at a time when their immune systems were immature and before they were vaccinated against the measles virus. One patient was immunocompromised, with vertically acquired HIV infection. All the children presented with cognitive and behavioural decline, abnormal movements and medically intractable myoclonic and tonic seizures. Outcome was poor in all and no reversibility was evident with standard therapeutic interventions. Optimal seizure control with carbamazepine is reported in patients with SSPE. Three of our patients who received carbamazepine experienced improved seizure control but, their neuroregression continued. Since submission of this case series, patient 1 (see Table 1) has died, and a further child has presented with the same clinical phenotype as described. On the basis of this clustering of patients in the Western Cape Province, SA, it is important to screen children admitted with acute cognitive decline and intractable seizures for SSPE, especially those who were infants during the measles outbreak.
**Case summaries**

Between April and June 2014, four children were admitted to Red Cross War Memorial Children's Hospital with intractable seizures and neuroregression (Table 1). All had previously been well, and they were aged between 4 years and 3 months and 4.5 years (median 4 years and 5 months) at presentation. Typical seizures consisted of recurrent myoclonic and atonic seizures. The atomic seizures manifested as 'head nods'. Cognitive function was progressively affected in all. Patient 3 had optic disc swelling at presentation, which remained static and was not associated with evidence of raised intracranial pressure. One of the children (patient 1) was immunocompromised as a result of HIV-1 infection, but had an undetectable viral load on antiretroviral therapy (ART).

CSF and serum analysis showed raised measles antibody titres, confirming the diagnosis of SSPE. Prior analysis with the polymerase chain reaction (PCR) for measles was negative on CSF in all, and initially led to the misleading assumption that the children did not have SSPE. Additional results included normal findings on CSF analysis and microscopy in all patients. CSF oligoclonal bands were positive in all the patients except patient 1. Findings on magnetic resonance imaging (MRI) (Figs 1A, 1B, 2A and 2B) varied from unremarkable at presentation, which remained static and was not associated with evidence of raised intracranial pressure. One of the children (patient 1) was immunocompromised as a result of HIV-1 infection, but had an undetectable viral load on antiretroviral therapy (ART).

Prior measles infection was rarely reported on routine history taking and had to be actively sought. Further questioning of the accompanying adults revealed that all the children had been infected with measles, either definitely or based on a history of a typical rash, between 3 months and 1 year of age. All would have received their first measles vaccination at 9 months of age, but were younger than this when they contracted measles.

Treatment in all children involved multiple combinations of antiepileptic drugs (AEDs), but with minimal response. However, improved control of myoclonic and atomic seizures was evident following the introduction of carbamazepine in three of the four children. Patient 3 remained on lamotrigine, as his seizures appeared to respond to this agent. In the management of patient 1, since carbamazepine is usually avoided in combination with ART, infectious diseases specialists were consulted; given the strong data supporting the use of carbamazepine in patients with SSPE, the drug was initiated and levels of both carbamazepine and ART closely monitored. To date no further complications have occurred and the patient has experienced improved seizure control.

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Fig. 1A. Patient 2. MRI of the brain (T2-weighted fluid attenuation inversion recovery (FLAIR)) 4 months after presentation. Imaging demonstrates nonspecific, bifrontal white matter foci of signal abnormality (a).

Fig. 1B. Patient 2. MRI of the brain (T2-weighted FLAIR) 8 months after presentation, demonstrating an interval progression of signal abnormality in the frontal lobes (a). The imaging shows high signal, and there is corresponding restricted diffusion in the deep white matter of both frontal lobes (a), the genu of the corpus callosum (b) and the right centrum semi ovale (c). The entire right temporal lobe is now swollen with high-signal white matter and blurring of the grey/white junction (d). This area is also restricted. The medial thalami and left parietal white matter are also involved (e).

Fig. 2A. Patient 3. MRI of the brain (T2-weighted FLAIR) 1 month after presentation, showing diffuse nonspecific small areas of hyperintensity scattered in the superficial and deep white matter in the frontal temporal lobes bilaterally, with no mass effect (a).

Fig. 2B. Patient 3. MRI of the brain (T2-weighted FLAIR) 6 months after presentation, showing marked interval deterioration with high signal in the white matter throughout the left cerebral hemisphere, most prominent in the parietal lobe (a). This also involves the posterior corpus callosum and posterior limb of the left internal capsule (b). Similar changes, but to a lesser extent were evident in the right parietal white matter. There was global volume loss within the left cerebral hemisphere, also involving the left cerebral peduncle and midbrain. In view of the previous measles infection, these findings were considered to be in keeping with SSPE with interval worsening.
<table>
<thead>
<tr>
<th>Patient No. (gender)</th>
<th>Age at presentation</th>
<th>Age when infected with measles</th>
<th>Presentation and evolution</th>
<th>Seizure types</th>
<th>EEG</th>
<th>Neuroimaging (MRI)</th>
<th>Measles virus PCR</th>
<th>CSF Ab* (mIU/ml)</th>
<th>Interventions (therapeutic and AEDs)</th>
<th>HIV</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>1 (M) 4 yr 5 mo. (April 2014)</td>
<td>4 yr 5 mo.</td>
<td>&lt;1 yr</td>
<td>1 wk Hx., seizures, low tone unsteadiness, cognitive regression</td>
<td>'Head nodding' – atonic seizures then myoclonic seizures</td>
<td>At 4/12 s burst-suppression in sleep. Myoclonic jerks on an encephalopathic background on awakening (Fig. 3)</td>
<td>Arachnoid cyst. Mild cerebellar atrophy. Thinning of splenium of corpus callosum</td>
<td>Neg.</td>
<td>73 453</td>
<td>Valproate, levetiracetam, clobazam, carbamazepine</td>
<td>Y</td>
<td>Poor Stage 3</td>
</tr>
<tr>
<td>2 (M) 4 yr 3 mo. (April 2014)</td>
<td>8 mo.</td>
<td>8 mo.</td>
<td>Seizures for 5 mo., but 1 mo. of evolving seizures and cognitive regression, then coma</td>
<td>Focal seizures then myoclonic and atonic seizures, GTCS</td>
<td>At 5/12 generalised spike and wave activity more marked over the left (Fig. 4)</td>
<td>At 6/12 frequent spikes and generalised polyspike and spike and wave activity on a severely encephalopathic background</td>
<td>Neg.</td>
<td>46 933</td>
<td>Sodium valproate, clobazam, lamotrigine, carbamazepine, phenobarbitone</td>
<td>N’</td>
<td>Poor Stage 4</td>
</tr>
<tr>
<td>3 (M) 4 yr 5 mo. (May 2014)</td>
<td>3 mo.</td>
<td>3 mo.</td>
<td>Prior viral illness, then acute 3-d history of falling, followed by a GTCS and unsteadiness. Then rapidly evolving seizures. Emotional lability with motor and cognitive regression. Swollen optic discs, which remained unchanged. Developed obtunded state with right hemiplegia</td>
<td>Myoclonic and atonic seizures, focal motor seizures</td>
<td>At presentation very slow background awake. Asleep recorded generalised and independent polyspike and spike and wave discharges</td>
<td>At 2/12 markedly abnormal with persistent spike and wave discharges associated with myoclonic jerks, compatible with electrical status (Fig. 5)</td>
<td>Neg.</td>
<td>19 845</td>
<td>Phenobarbitone, sodium valproate, clobazam, lamotrigine, pyridoxine, folinic acid</td>
<td>N</td>
<td>Poor Stage 3</td>
</tr>
<tr>
<td>4 (F) 4.5 yr (June 2014)</td>
<td>3 yr 6 mo.</td>
<td>3 mo.</td>
<td>GTCS with fever, 1 mo., later 'tics', abnormal movement then myoclonus, cognitive regression and behavioural difficulties</td>
<td>Myoclonic and atonic seizures</td>
<td>Slow background and period high-amplitude slow waves (Fig. 6a)</td>
<td>Normal at presentation</td>
<td>Neg.</td>
<td>28 745</td>
<td>Valproate, levetiracetam, clobazam, carbamazepine, isoprinosine</td>
<td>N</td>
<td>Poor Stage 3</td>
</tr>
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F = female; M = male; Hx = history; GTCS = generalised tonic–clonic seizures; Neg. = negative; Ab = antibody; Y = yes; N = no.

* Assay: Enzygnost anti-measles virus IgG (Siemens) (mIU) quantified according to the method described in the kit insert.

†HIV exposed.
seizure activity. Based on the four stages of the disease progression, as summarised in Table 2, three patients had reached stage 3 of the disease at the time of writing, and patient 2 was at the most severe stage 4. Patient 4 was commenced on isoprinosine after the product was imported from abroad with approval from the Medicines Control Council and the local pharmacy therapeutics committee. Motivations are in place for the remaining patients.

**Discussion**

In children aged <5 years, measles is the second most common cause of death due to a vaccine-preventable disease, and it is in the top ten causes of death due to infectious diseases. The World Health Organization predicts an increase in the numbers of measles cases and deaths as a result of logistical and financial challenges affecting vaccination coverage. In 2009, the US Centers for Disease Control published a report supporting this statement, and in the same year this is exactly what transpired in SA. Between 2009 and 2010, 28 African countries reported measles outbreaks. In Europe measles outbreaks were reported in 36 of the 53 European member states between 2009 and 2011, with the primary reason for the outbreaks reported to be failure to vaccinate susceptible populations. Vaccine safety concerns and perceived fewer benefits from vaccinations were found to be leading reasons for parents delaying vaccination of their children or refusing to vaccinate. The USA, which had declared itself ‘measles eliminated’ in 2000, issued a warning in 2014 of disease recrudescence due to imported cases. It can be concluded that this vaccine-preventable disease is far from contained.

There are three neurological complications following measles virus infection: acute disseminated encephalomyelitis, MIBE and SSPE. SSPE affects immune-competent and immune-compromised hosts. The virus is present in the brain, and the incidence is reported to be 1/10 000, increasing to 1/2 500 in children who contracted measles under 5 years of age. As in our patients, the condition occurs more commonly in boys than in girls. The risk of central nervous system (CNS) infection is increased when infection with the measles virus occurs at a young age, especially <2 years, when the immune system is immature and residual maternal antibodies may still be present. This was the case for the patients reported in this case series, all of whom were known or believed to have been infected with measles before 9 months of age. The pathogenesis of SSPE is poorly understood. Although viral antigen and RNA are abundant in the brain in both MIBE and SSPE, fever is unusual and the virus is difficult, if not impossible, to culture from CNS tissue. Resource-poor settings tend to have a higher incidence of measles infection than high-income countries and carry a higher burden of SSPE, although the condition may not be readily diagnosed. It is not unusual for the diagnosis of SSPE to be challenging and delayed owing to preferential consideration of other diverse differential diagnoses. Over 78% of patients were misdiagnosed in one large study of 307 patients, with the median time to diagnosis of SSPE being 6 months (range 0.2 - 96). Similar challenges were evident with our patients. Even when the diagnosis was suspected, there were a number of barriers to diagnostic closure. Furthermore, in settings such as SA where there is a high burden of HIV infection, the

Table 2. Clinical stages of progression of SSPE

<table>
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<th>Stage</th>
<th>Clinical features</th>
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<tr>
<td>1</td>
<td>Mental deterioration accompanied by alterations in personality</td>
</tr>
<tr>
<td>2</td>
<td>Myoclonus and often seizures</td>
</tr>
<tr>
<td>3</td>
<td>Progressive neurological deterioration marked by rigidity</td>
</tr>
<tr>
<td>4</td>
<td>Optic atrophy, akinetic mutism and coma</td>
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*Fig. 3. EEG from patient 1 in sleep state 4 months after presentation, demonstrating profoundly attenuated background (b) with recurrent periodic generalised paroxysms (a) consistent with a burst suppression pattern.*

*Fig. 4. EEG from patient 2 in sleep state 4 months after presentation, demonstrating slow attenuated background and recurrent periodic generalised spike and wave (a) and polyspike discharges (b) with suppression in between discharges.*
incidence may be expected to be further increased. Children of HIV-infected mothers are at particular risk of acquiring measles early, even before 9 months of age, which is the recommended age for vaccination in resource-limited settings.[6]

The average time to onset of SSPE after measles is 6 - 10 years (range 1 - 24).[6] The onset is insidious and the diagnosis is often not suspected early in the disease.[6] All the children in our series presented before 6 years of age and the SSPE followed an aggressive course, rapidly reaching either stage 3 or 4 disease. Patient 3 presented with swelling of the optic discs, which was identified during his acute management when he presented with seizures and regression. This finding, in combination with positive oligoclonal bands, led to extended screening for antibodies related to anti-NMDA (N-methyl D-aspartate) receptor antibody encephalitis, which was negative. The association of ocular and visual manifestations is reported in SSPE and was found in 42.5% of patients with SSPE.[12,13] There are four stages to the disease, which are summarised in Table 2. Death occurs within months to years after onset.[6]

The diagnosis of SSPE is usually confirmed by a combination of elevated levels of antibody to measles virus in the serum and CSF and detection of characteristic periodic slow-wave complexes on an EEG.[6]

Numerous therapeutic agents, including amantadine, interferon, isoprinosine and ribavirin, have been used for treatment of SSPE. Evaluation of efficacy is difficult, as most cases are isolated and occur in small clusters.[6] The most commonly used regimen is a combination of isoprinosine and interferon-alpha, with some suggestion that this combination slows disease progression.[6] The latter intervention is not available in SA.

Turkey is in the unfortunate position of having significant experience in the condition. Guler et al.[15] reported 64 patients with SSPE, diagnosed at an average age of 12.3 years (range 5 - 17). None of the interventions attempted, including isoprinosine and interferon, altered the long-term outcome. Furthermore, there was no difference between those who received isoprinosine in isolation and those receiving isoprinosine and interferon in combination. Guler et al. commented on high levels of
consanguinity, and questioned whether an additional genetic modifying factor in their patients made them more susceptible to developing SSPE. A study from Karachi in Pakistan reported on 43 patients with similar developing SSPE. A study from Karachi in Pakistan reported on 43 patients with similar

Furthermore, it is widely accepted that SSPE cannot occur in the absence of direct infection with wild-type measles virus. The incidence of SSPE is directly related to the incidence of measles in a population, and has decreased dramatically since the introduction of measles vaccination.4 The four cases described here may represent only a proportion of the cases across SA. In addition, it is likely that the reported numbers of children infected during the measles outbreak are an underestimation, and further patients are therefore likely to present with SSPE. Children presenting with acute-onset intractable seizures, especially myoclonus and atonic seizures, and showing neuroregression should have a careful history of previous measles infection in infancy documented, and there should be a low threshold for screening for measles CSF antibodies.

Routine measles vaccination is the best approach for preventing SSPE.6 Measles vaccine is a live attenuated vaccine, and vaccine strains have not caused SSPE. Furthermore, it is widely accepted that SSPE cannot occur in the absence of direct infection with wild-type measles virus. The incidence of SSPE is directly related to the incidence of measles in a population, and has decreased dramatically since the introduction of measles vaccination.4 The four cases described here may represent only a proportion of the cases across SA. In addition, it is likely that the reported numbers of children infected during the measles outbreak are an underestimation, and further patients are therefore likely to present with SSPE. Children presenting with acute-onset intractable seizures, especially myoclonus and atonic seizures, and showing neuroregression should have a careful history of previous measles infection in infancy documented, and there should be a low threshold for screening for measles CSF antibodies.

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