

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 Nondo, 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 and analysed the screens undertaken to confirm the diagnosis of SSPE in these children. Brian Eley is head of the Paediatric Infectious Diseases Department in the Department of Paediatrics and Child Health, RCWMCH and Faculty of Health Sciences, University of Cape Town. He assisted 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 atonic 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.

S Afr Med J 2015;105(9):713-718. DOI:10.7196/SAMJnew.7788



Between 2009 and 2011, 18 431 laboratory-confirmed cases of measles were reported from the nine provinces of South Africa (SA) (cumulative incidence 3/100 000 population).^[1] The highest incidence was in children <1 year of age (603/100 000). The incidence in infants <6 months of age was 302/100 000, in those aged 6 - 8 months 1 083/100,000, and in those aged 9 - 11 months 724/100 000. Forty-eight per cent of the patients were <5 years of age, with the result that significant additional demand was placed on child health services.^[1] A single strain of measles virus (genotype B3) circulated throughout this outbreak.

Across SA in 2002, following the 'catch-up' campaign in 1996 - 1997, there was a 96% decrease in patients admitted with measles, and a 100% decline in reported deaths.^[2] When the outbreak in 2009 occurred, a nationwide mass vaccination campaign was therefore undertaken over a 2-week period in mid-April 2010. Concern was raised that, compared with the effectiveness of the previous vaccination campaign, the one in 2010 lacked the same uptake levels, with anecdotal reports of poor uptake on the part of some parents and schools.^[3]

As an immediate consequence of the measles outbreak, a cohort of eight HIV-infected patients with probable ($n=3$) or definite ($n=5$) measles inclusion body encephalitis (MIBE) were managed in the

neurology department at Groote Schuur Hospital, Cape Town, SA, between July and October 2010.^[4,5] MIBE manifests between 1 and 7 months after acute measles infection. Patients present with seizures, often epilepsy partialis continua, and altered cognitive awareness.^[6] The mortality rate is 85%, and survivors are left with significant neurosequelae. In the case series reported from the Western Cape Province, six of the eight patients died and all followed the clinical course reported above.^[4,5] The youngest confirmed patient was 14 years of age. Anecdotally, two additional children, aged 10 (male) and 11 (female) years and suspected to have MIBE, were managed at Red Cross War Memorial Children's Hospital, Cape Town, with a parallel clinical course and findings on neuroimaging; both these patients also had HIV infection. However, serum and cerebrospinal fluid (CSF) screening in these patients, and even brain biopsy in one patient, failed to identify the measles virus. Albertyn *et al.*^[4] suggested that additional cases of MIBE were probably occurring across the country, but were potentially not detected without screening for the virus or completing the required notifications; in addition, some patients may have died before reaching medical services.

Five years after the most recent (2010) measles outbreak in SA, a new cohort of children have presented with subacute sclerosing panencephalitis (SSPE).

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 atonic 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 to the typical nonspecific white matter hyperintensities described in SSPE.^[6] Electroencephalograms (EEGs) (Figs 3 - 6B) typically demonstrated generalised periodic spike, or polyspike, wave discharges with suppression of background activity, which were intermittent and correlated with seizure events. Serial studies confirmed progressive deterioration with increasingly suppressed background activity.

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 atonic seizures was evident following the introduction of carbamazepine in three of the four children. Patient 3 remained on lamotrigine, as his seizures appeared to

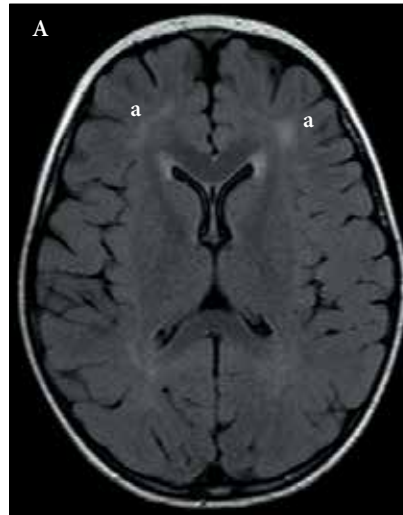


Fig. 1A. Patient 2. MRI of the brain (T2-weighted fluid attenuation inversion recovery (FLAIR)) 4 months after presentation. Imaging demonstrates nonspecific, bifrontal white matter foci of signal abnormality (a).

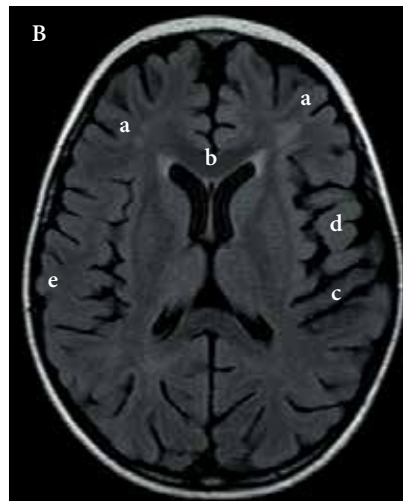


Fig. 1B. Patient 2. MRI of the brain (T2-weighted FLAIR) 8 months after presentation, demonstrating an interval progression of signal abnormality in the frontal lobes (a). The imaging shows high signal, and there is corresponding restricted diffusion in the deep white matter of both frontal lobes (a), 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).

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

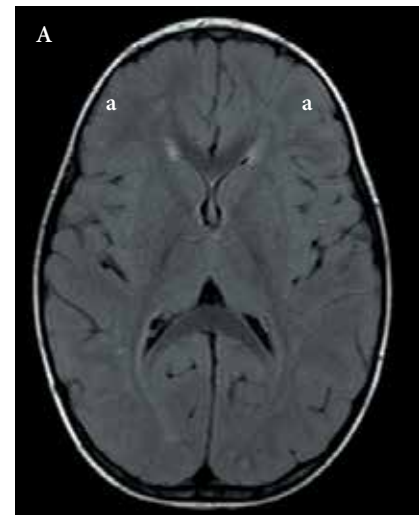


Fig. 2A. Patient 3. MRI of the brain (T2-weighted FLAIR) 1 month after presentation, showing diffuse nonspecific small areas of hyperintensity scattered in the superficial and deep white matter in the frontal temporal lobes bilaterally, with no mass effect (a).



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.

carbamazepine and ART closely monitored. To date no further complications have occurred and the patient has experienced improved seizure control.

All the patients had progressive neurocognitive regression, loss of ambulation and speech, feeding dependency and frequent

Table 1. Demographics of the children with SSPE, and clinical findings

Patient No. (gender)	Age at presentation	Age when infected with measles	Presentation and evolution	Seizure types	EEG	Neuroimaging (MRI)	Measles virus PCR	CSF Ab* (mIU/ml)	Interventions (therapeutic and AEDs)	HIV	Outcome
1 (M)	4 yr 5 mo. (April 2014)	<1 yr	1 wk Hx, seizures, low tone unsteadiness, cognitive regression	'Head nodding' - atonic seizures then myoclonic seizures	At 4/12 s burst-suppression in sleep. Myoclonic jerks on an encephalopathic background on awakening (Fig. 3)	Arachnoid cyst. Mild cerebellar atrophy. Thinning of splenium of corpus callosum	Neg.	73 453	Valproate, levetiracetam, clobazam, carbamazepine	Y	Poor Stage 3
2 (M)	4 yr 3 mo. (April 2014)	8 mo.	Seizures for 5 mo., but 1 mo. of evolving seizures and cognitive regression, then coma	Focal seizures then myoclonic and atonic seizures, GTCS	At 5/12 generalised spike and wave activity more marked over the left (Fig. 4) At 6/12 frequent spikes and generalised polyspike and spike and wave activity on a severely encephalopathic background	At 8/12 nonspecific bifrontal foci of signal abnormality (Fig. 1a) At 9/12 progression of the frontal lobes, swollen right temporal lobe, involvement of medial thalami and left parietal lobe (Fig. 1b)	Neg.	46 933	Sodium valproate, clobazam, lamotrigine, carbamazepine, phenobarbitone	N [†]	Poor Stage 4
3 (M)	4 yr 5 mo. (May 2014)	3 mo.	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	Myoclonic and atonic seizures, focal motor seizures	At presentation very slow background awake. Asleep recorded generalised and independent polyspike and spike and wave discharges At 2/12 markedly abnormal with persistent spike and wave discharges associated with myoclonic jerks, compatible with electrical status (Fig. 5)	At presentation nonspecific diffuse, small white matter T2 and FLAIR hyperintensities in the superficial and deep areas bifrontally (Fig. 2a) At 5/12 progression with T2/FLAIR white matter hyperintensities throughout left hemisphere more than right. Involvement of posterior corpus callosum and posterior internal capsule on the left. Global volume loss with left cerebral hemispheric and cerebral peduncle predominance (Fig. 2b)	Neg.	19 845	Phenobarbitone, sodium valproate, clobazam, lamotrigine, pyridoxine, folic acid	N	Poor Stage 3
4 (F)	4.5 yr (June 2014)	3 mo.	GTCS with fever, 1 mo., later 'tics', abnormal movement then myoclonus, cognitive regression and behavioural difficulties	Myoclonic and atonic seizures	Slow background and period high-amplitude slow waves (Fig. 6a) At 1/12 slow background, frequent generalised polyspike and wave discharges (Fig. 6b)	Normal at presentation	Neg.	28 745	Valproate, levetiracetam, clobazam, carbamazepine, isoprinosine	N	Poor Stage 3

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 α-method described in the kit insert.
[†]HIV exposed.

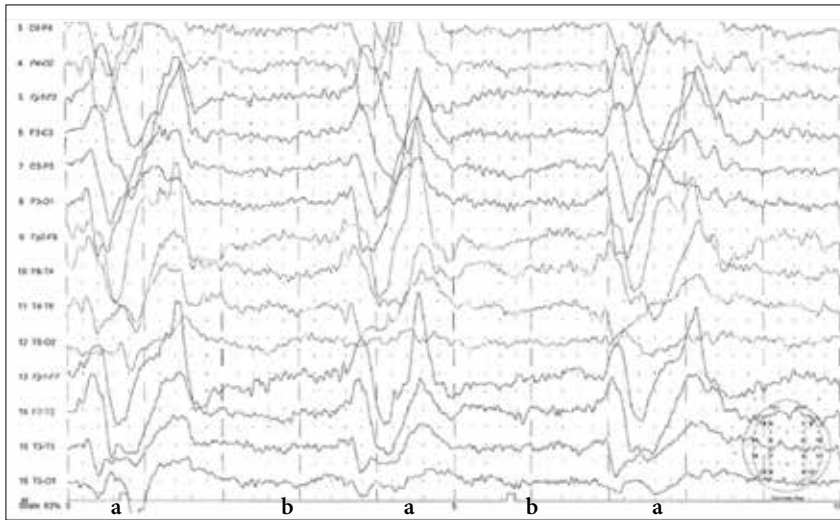


Fig. 3. EEG from patient 1 in sleep state 4 months after presentation, demonstrating profoundly attenuated background (b) with recurrent periodic generalised paroxysms (a) consistent with a burst suppression pattern.

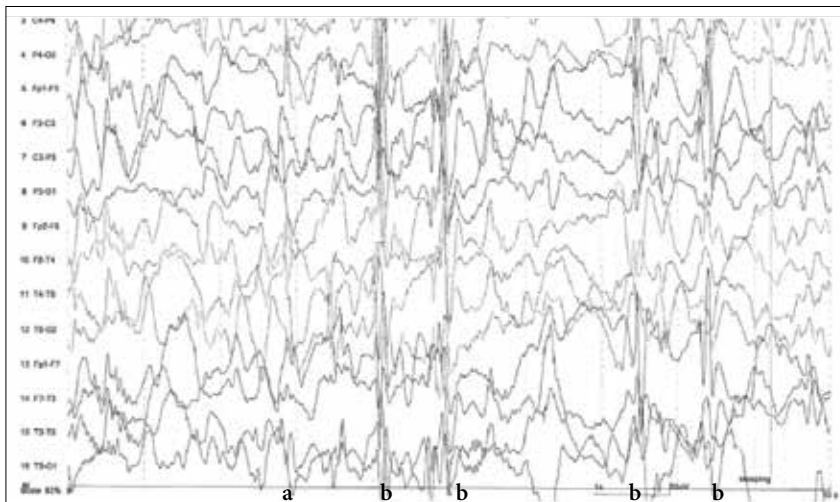


Fig. 4. EEG from patient 2 in sleep state 4 months after presentation, demonstrating slow attenuated background and recurrent periodic generalised spike and wave (a) and polyspike discharges (b) with suppression in between discharges.

Table 2. Clinical stages of progression of SSPE^[6]

Stage	Clinical features
1	Mental deterioration accompanied by alterations in personality
2	Myoclonus and often seizures
3	Progressive neurological deterioration marked by rigidity
4	Optic atrophy, akinetic mutism and coma

in 2014 of disease recrudescence due to imported cases.^[11] 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.^[6]

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.^[6] As in our patients, the condition occurs more commonly in boys than in girls.^[6] 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.^[6] 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.^[6] 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).^[6] 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

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.^[6] 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.^[7] 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.^[1,7] Between 2009 and 2010, 28 African countries reported measles outbreaks.^[8] 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.^[9] 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.^[10] The USA, which had declared itself 'measles eliminated' in 2000, issued a warning

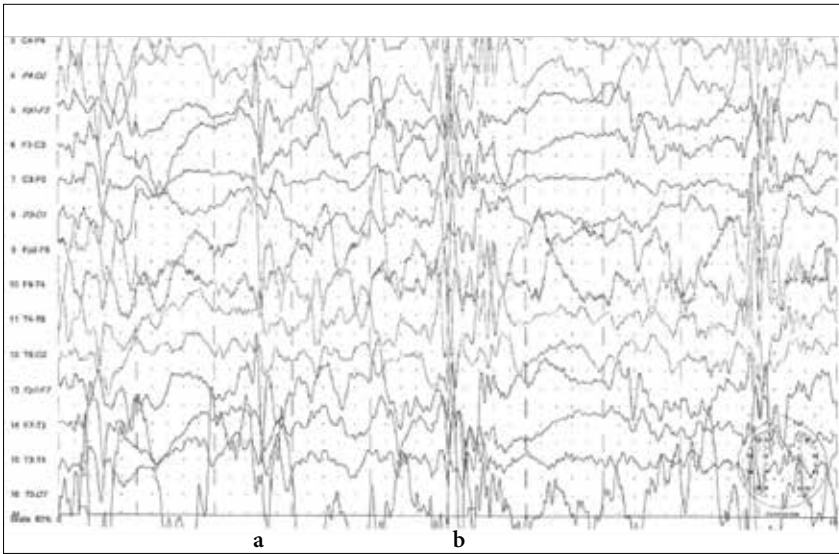


Fig. 5. EEG of patient 3 in sleep state 2 months after presentation, showing a markedly abnormal recording with persistent spike and wave discharges (a) associated with myoclonic jerks and suppression (b) and compatible with electrical status.

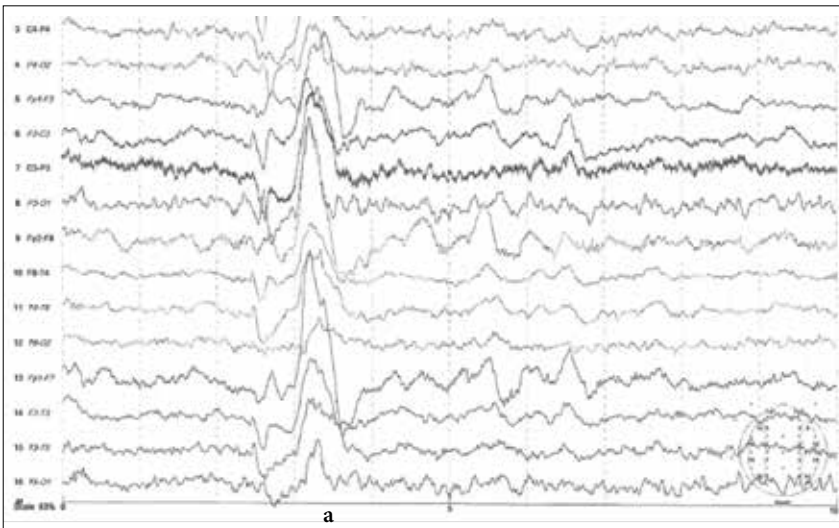


Fig. 6A. Patient 4. EEG at presentation in sleep state, demonstrating a slow attenuated background with a generalised high-amplitude slow wave (a) which occurred periodically throughout the recording.

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 in one study; the optic disc swelling in our patient 3 was in keeping with a diagnosis of 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] The EEGs (Figs 3 - 6) in our patients were

helpful and supportive of the diagnosis of SSPE. Neuroimaging is generally unhelpful, findings often being normal in the early stages of the disease, and the focal or diffuse T2-weighted hyperintense lesions that appear later are not pathognomonic.^[6] This was the case in our patients; even patient 3, who developed extensive white matter hyperintensities, would have had a wide range of differential diagnoses without the finding of raised CSF measles antibodies that supported a diagnosis of SSPE. While in our patients the seizure presentation was a major indicator of a more complex condition, all had been well before their abrupt onset of cognitive dysfunction and seizures. Their seizures were very stereotyped, persistent and resistant to typical medical interventions. Despite relatively early suspicion of SSPE, the initial lack of history of infection and negative CSF PCR results were misleading. It was only with persistence (largely on the part of author AN) that the history of prior measles infection was confirmed in all, after which pursuit of the correct screening in the CSF, namely the measles antibody titres, enabled the diagnosis to be confirmed. Viral nucleic acid is rarely found in the CSF of patients with SSPE.^[14] This is due to absence of a typical productive infection of the brain with extracellular release of virus. In the case of patients with SSPE, only the genome and nucleocapsid replicates and these spread from cell to adjacent cell through membrane fusion across synapses. Viral nucleic acid will therefore only be present in infected cells. Findings were similar in the patients reported with MIBE, of whom only two were PCR-positive in the CSF.^[5]

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

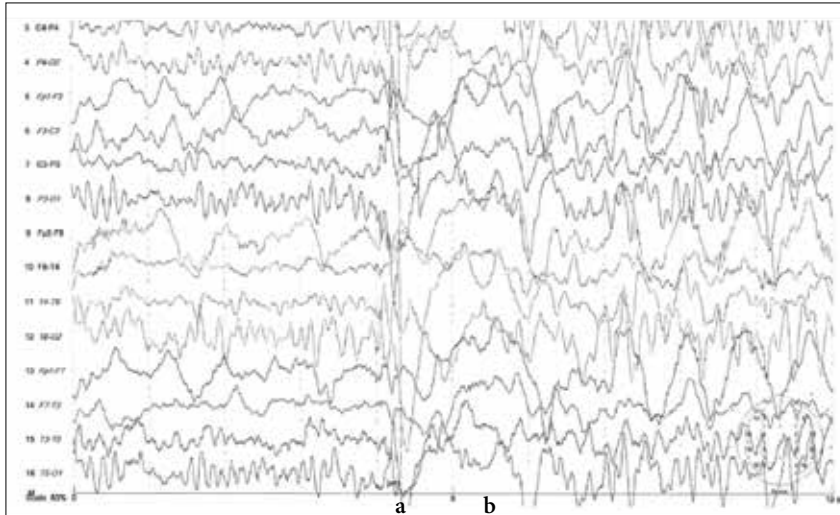


Fig. 6B. Patient 4. Follow-up EEG at 1 month in awake state, demonstrating normal posterior alpha rhythms with overriding 2 Hz generalised slow waves and periodic spike and slow wave (a) followed by 2 seconds of attenuation (b). This discharge correlated with a myoclonic seizure and was recurrent throughout the recording.

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 clinical findings and outcomes.^[16]

There are several implications for management, which is significantly determined by confirmation of the diagnosis, beyond the importance to the family of having diagnostic closure. Presentation with myoclonic or atonic seizures would normally preclude the use of carbamazepine, but for patients with SSPE this agent has the best seizure efficacy.^[17-20] For our patient with HIV this led to further complications relating to the need for more aggressive monitoring of his HIV viral titres and the carbamazepine levels, owing to the risk of cross-reactivity with ART. An alternative agent could have been levetiracetam, but in fact careful monitoring of drug levels enabled carbamazepine to be used successfully. There are no data in the literature to guide a treatment care plan in the setting of SSPE and the immunocompromised patient, and colleagues in Turkey had not managed such a case (personal communication, B Anlar). This scenario is likely to be a uniquely African challenge.

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.^[6] 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.^[6]

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 prior measles infection in infancy documented, and there should be a low threshold for screening for measles CSF antibodies.

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Accepted 18 December 2014.