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Case Report and Molecular Analysis of Subacute Sclerosing Panencephalitis in a South African Child

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This is the first case of subacute sclerosing panencephalitis from South Africa in which the molecular characteristics of the causative measles virus were examined. The virus found is classified as genotype D3, which has not previously been found in Africa and was last circulating in the United States before 1992.

Subacute sclerosing panencephalitis (SSPE) is a rare, chronic neurological disease of children and adolescents resulting from persistent measles virus (MV) infection of brain cells. SSPE generally develops 5 to 10 years after acute measles, starting with subtle signs of intellectual and psychological dysfunctions and continuing with sensory and motor function deterioration and progressive cerebral degeneration, leading to death after a period of months or years (14). Various mechanisms of this persistent MV infection of the brain have been suggested, including the presence of defective viral particles and alterations in viral gene expression, particularly hypermutations and deletions in some of the viral genes (11).

The significant epidemiological characteristics of SSPE cases in all the published South African papers to date are shown in Table 1. The reported incidence of SSPE in South Africa ranges from 2.6 cases/1,000,000 people per year in the earlier studies (7, 8), before the introduction of universal measles immunization, to 0.39 case/1,000,000 people per year in the later studies (2, 9). The most recent South African SSPE incidence figure of 0.43 case/1,000,000 people per year (3) is lower than the global estimate of 1 case/1,000,000 people per year (11). Furthermore, although the earlier South African SSPE studies showed a clear racial and geographical distribution of cases, with the highest prevalence of SSPE being found in children of mixed race from the Cape Province (7–9), subsequent studies show no racial differences in SSPE incidence. The rate of occurrence of SSPE disease in black children (0.39 case/1,000,000 people per year) is not significantly different from that in white children (0.63 case/1,000,000 people per year) (13). However, distinct clustering of SSPE cases within South Africa in the Cape Province, first noted between 1970 and 1975 (8), continues to be demonstrated. The Cape Province consistently shows a higher prevalence of SSPE cases than the rest of the country and the Southern African region (4, 7–9). Other epidemiological features of SSPE in South Africa include an almost equal male-to-female distribution of cases, with a male/female ratio of 0.9:1 (9), which is not consistent with the male predominance of SSPE found in studies from other countries (11). Also, most South African children demonstrate acute measles infection at an early age: at least 42% of SSPE patients have natural measles infection before the age of 1 year (4, 10), with a median age of 11.1 years at SSPE onset (13).

We describe here the clinical features and molecular characteristics of a single case of SSPE in a child from South Africa. To genotype the MV in this case, we amplified viral genomic material from the 3′ terminus of the nucleocapsid (N) gene from both cerebrospinal fluid (CSF) and blood. This is the genomic region most commonly used to genotype MV in molecular epidemiological studies (2).

Informed consent was obtained from the parents of the subject. Clearance from the Committee for Research on Human Subjects and Ethics at the University of the Witwatersrand, Johannesburg, South Africa, has been obtained for this work, protocol M960201. Human experimentation guidelines as specified by this committee were followed in the conduct of the clinical research.

Case report. In March 1997 a black female child aged 4 years, 10 months, was referred for further investigation to the Red Cross Children's Hospital (Cape Town, South Africa) from Port Elizabeth (Eastern Cape Province, South Africa) after she had failed to respond to treatment for epilepsy, her initial diagnosis. According to her mother, the child had been well until January 1997, at which time she noticed that the child was "falling" while playing. These episodes increased in frequency and severity over the next 2 months, with the child falling to the ground after every few steps. There was no history of classical seizures or change in mental status. Also, there was no clear history of natural measles infection, and the mother thought the child had received all her childhood immunizations.

On physical examination, the child's general health was good and her height, weight, and head circumference were all in the 3rd centile. During the examination she had numerous myoclonic "head nods" and loss of tone associated with momentary disturbances in consciousness. In between these episodes she was orientated to time, place, and person. Her cranial nerves, reflexes, and other motor, sensory, and cerebellar functions were normal. There were no abnormalities in blood samples taken for full blood count and differential or for urea and electrolytes; however, her total immunoglobulin G (IgG) in plasma was mildly raised at 17.7 g/liter (normal range, 5.4 to 14.4 g/liter). Peripheral blood was positive for MV-specific IgG and negative for IgM antibodies by enzyme-linked immunosorbent assay (measles ELISA, Behring, Berlin, Germany). Pa-

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TABLE 1. Summary of epidemiological characteristics of described SSPE cases from published South African studies

Reference	Yr of data collection	Area	Total no. of cases	SSPE incidence[a]	No. of cases by race	Age (yr)	Male/female ratio
8	1971–1974	Cape Province	15	1.2	9 M, 6 B	3–13	2.8:1
7	1955–1974	Southern Africa[b]	79	ND	36 W, 23 M, 20 B	1–23	ND
4	1955–1975	Southern Africa[b]	96	M, 15.9[c]; W, 2.9[c]	30 W, 30 M, 26 B	1–23	2.2:1 (W), 0.9:1 (M), 1.8:1 (B)
9	1955–1980	Southern Africa[b]	116	M, 2.6[c]; W, 1.47[c]	ND	ND	ND
3	1984–1987	South Africa	44	Overall, 0.43; W, 0.63; B, 0.36	12 W, 32 B	3–27	0.9:1
13	1984–1990	South Africa	75	ND	16 W, 5 M, 53 B	2–29	1:1.1
10	1982–1987	Kwazulu-Natal Province	18	ND	17 B, 1 A[d]	4–14	1.25:1

[a] Number of cases per 1,000,000 people per year. W, white; M, mixed; B, black, ND, not done.
[b] Includes Zimbabwe, Namibia, and Malawi.
[c] Age-specific (0 to 24 years) incidence, Cape Province only (1970 to 1976).
[d] A, Asian.

rental consent was obtained for human immunodeficiency virus antibody testing, which gave a negative result. A lumbar puncture was performed; the CSF pressure, chemistry, and cytology were normal, and microbiological cultures were all negative. Two abnormalities were found in the CSF: a raised total immunoglobulin of 49 mg/ml and the presence of IgG MV antibodies upon both immunofluorescence testing (CSF titer > 80 U) and enzyme-linked immunosorbent assay (Measles IgG ELISA, Behring).

An electroencephalogram showed a severe epileptiform pattern with a generalized spike and slow-wave paroxysms at 4-s intervals. Although not diagnostic of SSPE, this feature is highly suggestive of the condition. A computerized-tomography scan showed atrophy of the frontal lobes and slight dilatation of the lateral ventricles. A magnetic-resonance-imaging scan confirmed these findings and showed symmetrical demyelination in both frontal regions with periventricular extension. Based on the above findings, a diagnosis of SSPE was made. The child's condition remained unchanged during her stay in the hospital. She did not respond to anticonvulsant therapy and continued to have myoclonic head nods every few seconds. In April 1997 she was discharged to the referring hospital with a poor prognosis. The child was subsequently lost to follow-up, and no details regarding outcome are available.

Further investigations of blood and CSF specimens. To explore the characteristics of the MV causing SSPE in this patient, viral RNA was extracted from both blood and CSF specimens and amplified by reverse transcriptase PCR by using a technique which has been described previously (5). MV-specific primers from two overlapping fragments of the 3′ terminus of the N gene (375 and 384 bp, respectively) were used (6). Both serum and CSF yielded identical sequences of the 3′ terminus of the MV N gene. There was no evidence of any hypermutations or deletions in this gene. Sequence analysis of the N gene placed the virus from this case into genotype D3, clade D (6).

Discussion. This is the first report of SSPE from South Africa with genetic characterization of the causative virus. The D3 viral genotype identified in this case has never been found in Africa before. Previously it has been shown that MVs from three genotypes (A, D2, and D4) have been circulating in South Africa since 1978, with genotype D4 representing the major genetic group (5). However, the virus associated with this case of SSPE clearly belonged to genotype D3, based on the N gene sequences identified. The last documented indigenous circulation of wild-type D3 MV occurred in the United States in 1992 (2). It is possible that the D3 genotype exists as a minor genotype in South Africa that has so far evaded the MV molecular epidemiological surveillance done in this country, as these studies have not directly examined the circulating viruses from the Eastern Cape, where this child lived. Alternatively, this child may have been exposed to the D3 virus through contact with an infected person who travelled to South Africa from another country. The pathway of transmission is impossible to establish at this stage.

SSPE-associated MV has been characterized in a number of studies from various geographical areas of the world, including Europe (Spain, Germany, and Northern Ireland), the United States, and Japan (12). Although the epidemiology of measles in these developed countries, which have largely interrupted the circulation of wild-type MV, is markedly different from that in South Africa, where measles is endemic, the annual incidence of SSPE in Europe is estimated to be higher, between 1 in 300,000 and 1 in 25,000 (11). The SSPE viruses from Spain have been grouped into one genotype (group F), but most of the other SSPE-associated MVs have been placed into different genotypes, including C1 and D1 (15). The characteristics of the latter viruses are similar either to those of the current circulating wild-type MV isolates or to those of viruses that circulated as early as 10 years previously in these geographical regions (1).

Although it was originally proposed that infection with specific, mutant MV strains different from the circulating wild-type MV were associated with SSPE, it is now clear that this is not the case and that SSPE mutations are associated with adaptation of MV for long-term infection of the human brain after an initially normal wild-type infection (11). Many of these SSPE mutations affect the envelope-associated antigens (hemagglutinin [H]) and the matrix (M) protein, but no distinctive biological markers that can be applied to all SSPE viruses have been described yet (1). No unusual deletions, insertions, or hypermutations were found in the analysis of the 3′ terminus of the N gene from this case. Therefore, the virus causing SSPE in this child did not demonstrate any abnormalities in N gene expression, and a wild-type MV, not a vaccine virus, was associated with SSPE. However, there was insufficient genetic material available to amplify other genes of interest in SSPE (M and H) for this case; therefore, we cannot comment on their genetic structure at this time. Further investigations of these findings must be done in other cases of SSPE from South Africa.

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