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CASE REPORTS

Subacute measles encephalitis: A case of long term survival with follow-up MR brain scans

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Abstract

Measles virus causes three distinct neurological syndromes: acute disseminated encephalomyelitis, subacute sclerosing panencephalitis and the rare subacute measles encephalitis, or inclusion body measles encephalitis. There is a current debate of whether subacute measles encephalitis is an opportunistic infection or a subacute infection caused by a mutated measles strain. There is also no report of long term MRI of survivor. We reported a young Chinese girl with a history of relapsed acute lymphoblastic leukaemia and subacute measles encephalitis confirmed by brain biopsy who survived. Serial magnetic resonance imaging of the brain showed cortical and basal ganglial involvement in the initial phase, and generalized cerebral atrophy in the subsequent scan four and a half years later. The patient recovered from subacute measles encephalitis with substantial neurological deficits with the cessation of maintenance chemotherapy without specific antiviral treatment. This suggested that reconstitution of host immunity was adequate in effecting the clearance of the virus, and supporting the hypothesis that subacute measles encephalitis is primarily an opportunistic infection.

INTRODUCTION

Measles virus affects the central nervous system (CNS) in three distinct clinical syndromes, namely acute disseminated encephalomyelitis, subacute sclerosing panencephalitis (SSPE), and subacute measles encephalitis (SME) or measles inclusion body encephalitis. Acute measles encephalitis often occurs during convalescence from acute measles infection and presents with recurrence of fever, headache, seizure, changes in conscious state and variable neurological deficits.[1-3] It is generally believed to be an autoimmune reaction to measles virus, though more recent studies had proposed a direct viral invasion of the CNS as the mechanism.[2] SSPE on the other hand, presents after a long latent period of 6 to 8 years, usually in otherwise healthy children, with insidious intellectual deterioration, behavioural changes, later progressing to myoclonic jerks, spastic quadriparesis, deterioration in conscious state and eventual death.[3,4] SME is a rare condition, usually presenting in children with lymphoid malignancies with partial seizure or epilepsia partialis continua, altered conscious state and variable neurological deficits.[1] Overall mortality is 85%[1]; with 76% of all patients dying from SME itself[5], while the rest from the underlying disease. SME rarely occurs in immunocompetent adults [6] and could result from vaccination with live attenuated virus in immunosuppressed hosts.[5] There is as yet no report of long-term survivors of SME with follow-up brain MRI in the literature. We report here a patient who survived an episode of SME following acute lymphoblastic leukaemia.

CASE REPORT

An ethnic Chinese girl born in 1988 was diagnosed to have acute lymphoblastic leukaemia (ALL) in 1992 when she was 4 years old. Her antenatal, postnatal and developmental history was normal. She completed her immunisation on schedule at one year of age, and this included mumps, measles and rubella vaccinations. She completed chemotherapy and went into remission in 1994.

During a routine follow up on July 1998, she was found to be pale, with blood pressure of 110/60 mmHg, heart rate of 100 beats per-minute and temperature of 37^{O}C. She had no bruises, and

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examination of the cardiovascular, respiratory and abdominal systems was normal. There were no focal neurological deficits. Her peripheral blood examination showed 10% blast cells. The haemoglobin was 7.3 g/dl, total white cell count was 2, 900 X 10^6/l, and the platelet count was 180,000/µl. A bone marrow examination confirmed bone marrow relapse of ALL type L2 with 80% blast cells. Cerebrospinal fluid examination, chest x-ray, renal function test and echocardiogram were normal. She was started on British-French-American (BFM)-relapse protocol.

On November 1999, while she was still taking 6-thioguanine 20 mg daily, methotrexate 12.5 mg weekly and co-trimoxazole 80 mg thrice a week, she was admitted with a one day history of high fever, sore throat, runny nose and productive cough with white sputum. On examination, her temperature was 38.6°C, and she had inflamed oropharynx and tonsillar exudates. Respiratory examination and chest x-ray were normal. The haemoglobin was 13g/dl, white cell count 2,900 X 10^6/l and platelet was 92, 000/µl. She responded to intravenous amikacin and ceftazidime, and was discharged well 10 days later.

On March 2000, she presented again with generalized weakness, slowness of mentation, slow and slurred speech for one week before admission, and focal twitching of the right side of the face for about 5 minutes on the day of presentation. On examination, she was alert, conscious, oriented and apart from left facial nerve palsy, she had no other neurological deficits. Laboratory examination showed that her serum sodium, calcium, magnesium, glucose, creatinine and liver function tests were all normal. A cerebrospinal fluid (CSF) examination done on the day of admission showed protein level of 0.44 g/l, glucose of 3.1 mmol/l, with no cells or organism. Two days later, she developed twitching on both sides of her face. Five days later, the twitching stopped, but she was slow in responding to verbal cues and had expressive dysphasia. A week after admission, she developed focal seizures on the right upper limb as well as choreiform movements of the same limb at other times. Electroencephalography (EEG) done on the same day showed diffuse slow waves of 2 to 5 cycles per-second with multifocal discharges, occurring more on the left side. An MRI of the brain showed several high signal FLAIR and T2W confluent lesions along the left temporal and both frontal gyrus. There were also involvement of the left caudate and putamen region (Figure 1).

She was treated with phenytoin, but developed visual hallucination and confusion the same night. Another EEG done 9 days after admission showed high voltage slow waves of 1 to 2.5 cycles per-second on the left hemisphere, and 3 to 5 cycles per-second on the right, with high amplitude sharp waves localized to the left side. Phenytoin was stopped and she was treated with clonazepam and acyclovir. A repeat CSF examination 12 days after admission showed 26 polymorphs /µl, no lymphocytes or organisms demonstrated on Gram stain, protein level of 0.39 g/l and glucose of 3.4 mmol/l. Serology for antibodies against measles, rubella, Nipah and herpes simplex viruses was performed on the cerebrospinal fluid and serum, and only IgG for measles was positive in both fluids. A fortnight after admission, her condition stabilized with only occasional twitching of her upper limbs. A brain biopsy was performed on 11th April 2000, 26 days after admission.

The brain biopsy tissue obtained from the left temporal lobe was fixed in 10% formalin, routinely processed and embedded in paraffin. Histological examination showed meningoencephalitis in the cerebral cortex with eosinophilic viral inclusions in neuronal cytoplasm, as well as nuclear inclusions. In the brain parenchyma there was evidence of mild to moderate infiltration by microglia and other inflammatory cells, perivascular cuffing by lymphocytes, macrophages and the occasional plasma cell. The overlying meninges showed mild meningitis. Immunohistochemistry using a standard immunoperoxidase[7] method performed with a specific anti-measles primary antibody on tissue sections confirmed the presence of measles viral antigens (Figure 2).

She was discharged a week after the biopsy with clonazepam and phenobarbitone. Her chemotherapy was stopped prematurely. On follow-up, she was noted to deteriorate neurologically slowly until May 2004 when her condition was at a plateau. She remained wheelchair bound, and did not maintain eye contact or any meaningful communication. She had occasional seizure that was controlled with clonazepam and sodium valproate. A repeat brain MR scan was done on August 2004, almost 4 ½ years after the onset of the initial focal seizure, which showed generalized cerebral atrophy. There are also encephalomalacic changes with gliosis in the previously noted hyperintense lesions seen on the first scan. This was likely to represent the scar from previous brain biopsy (Figure 3). She was last seen in October 2005 when she remained in a vegetative state but had no more seizure and no further deterioration.

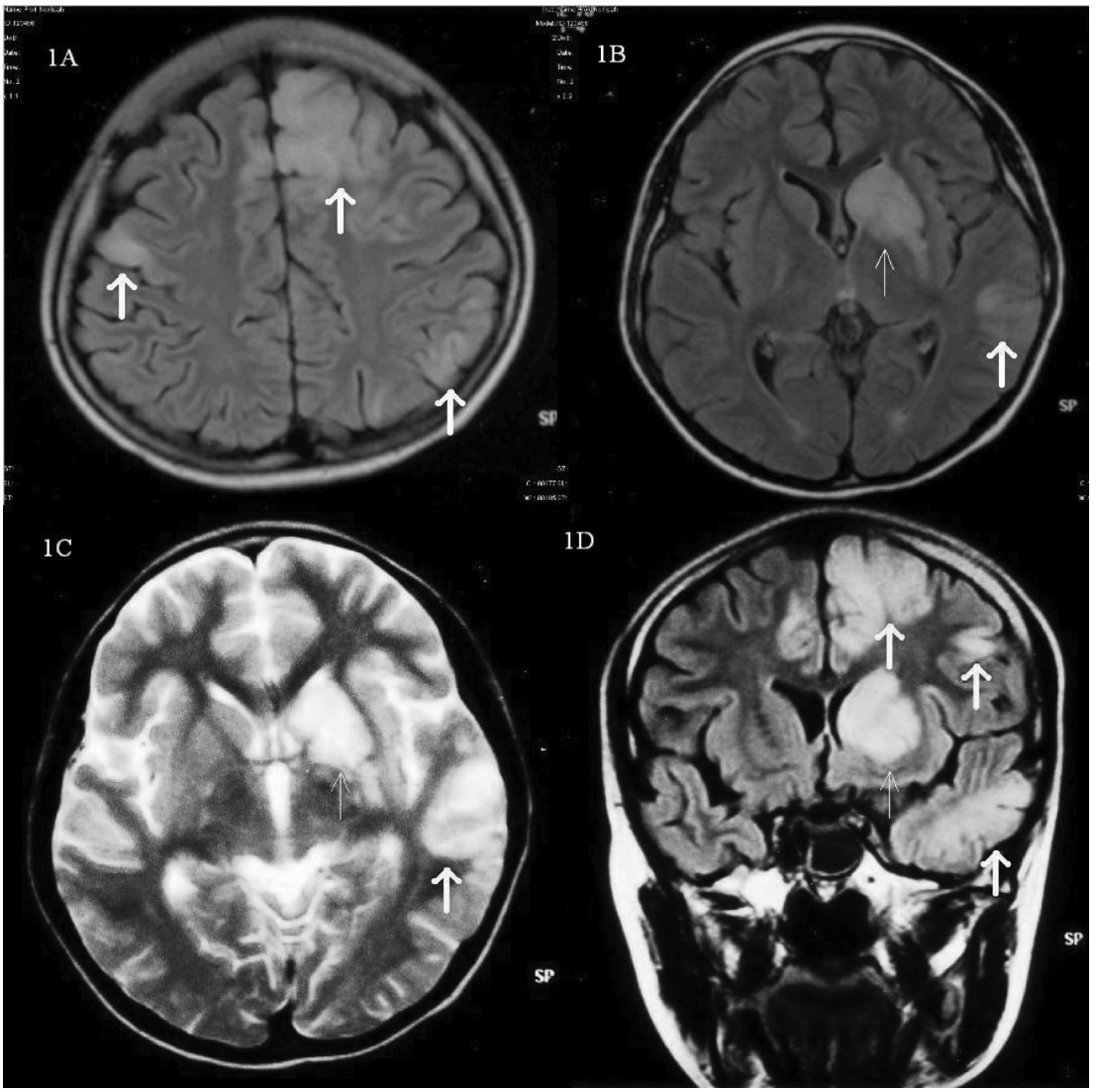

Fig. 1: MRI FLAIR axial sequence (figure 1A and 1B), T2 weighted axial image (figure 1C) and FLAIR coronal sequence (figure 1D) showing confluent gray matter (thick arrows) and left caudate nucleus and putamen involvement (thin arrows).

DISCUSSION

Our patient did not have acute disseminated encephalomyelitis or other infections of the central nervous system because measles viral antigens were shown to be present in her brain biopsy sections. The histopathological findings were typical of SME. The use of immunohistochemistry to confirm the diagnosis of measles infection has been described previously, and has been widely accepted for this purpose.[3,5,6,8-10] She had SME and not SSPE because the clinical onset was relatively rapid. She had choreiform movement of the limbs and partial seizures instead of myoclonus as seen in SSPE. Focal or multifocal motor seizure is a common features in patients with SME, seen in up to 78%.[1,5,8,9] The EEG pattern of diffuse slow waves and focal discharges is a well documented finding in SME, unlike the periodic complexes associated with myoclonus in SSPE.[1,8] The fact that she survived the illness and the disease remained stable with no active clinical or radiological progression for more than 5 ½ years is also an unusual feature of SSPE. SME is reported to have a mortality of 76%, compare with 95% or more in SSPE.[1,4]

Our patient is unique because there are very few long term follow-up studies of SME. To our knowledge this is the first documented long term survivor with serial MR findings. The initial

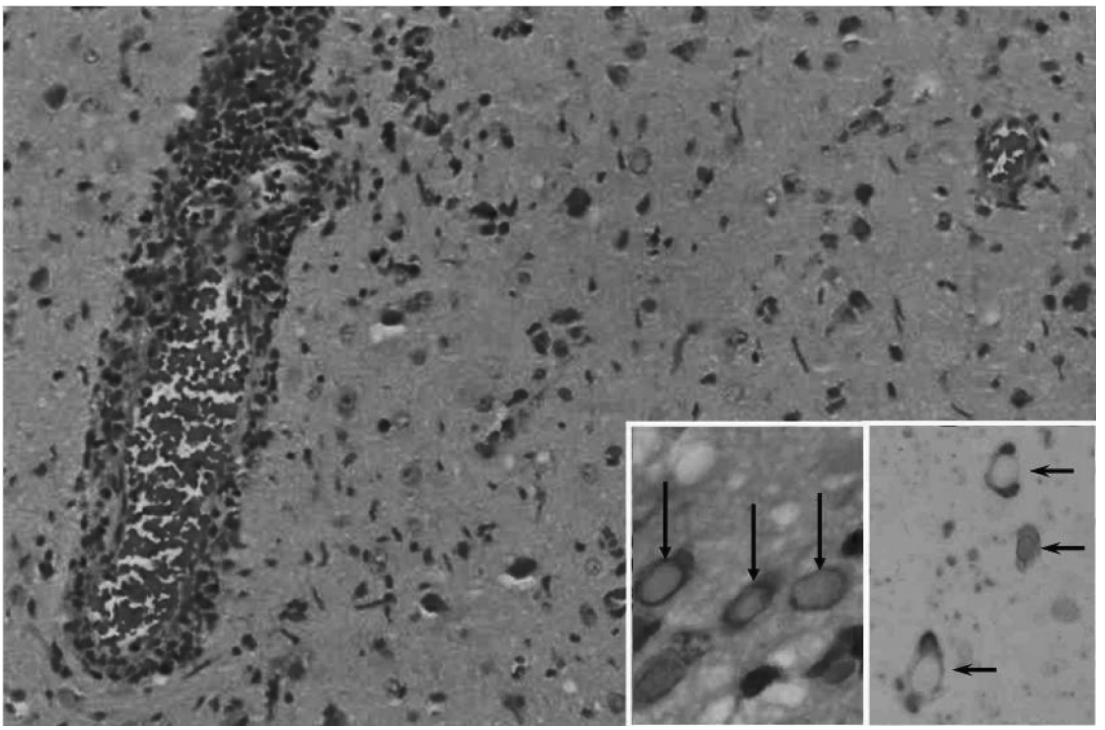

Fig. 2: Hematoxylin and eosin stains showing perivascular cuffing by mononuclear cells, microglial infiltration, eosinophilic viral inclusions in neuronal cytoplasm (long vertical arrows in the inset) and on immunohistochemical staining, the presence of viral antigens as detected by anti-measles antibody with immunoperoxidase reaction (short horizontal arrows in the inset).

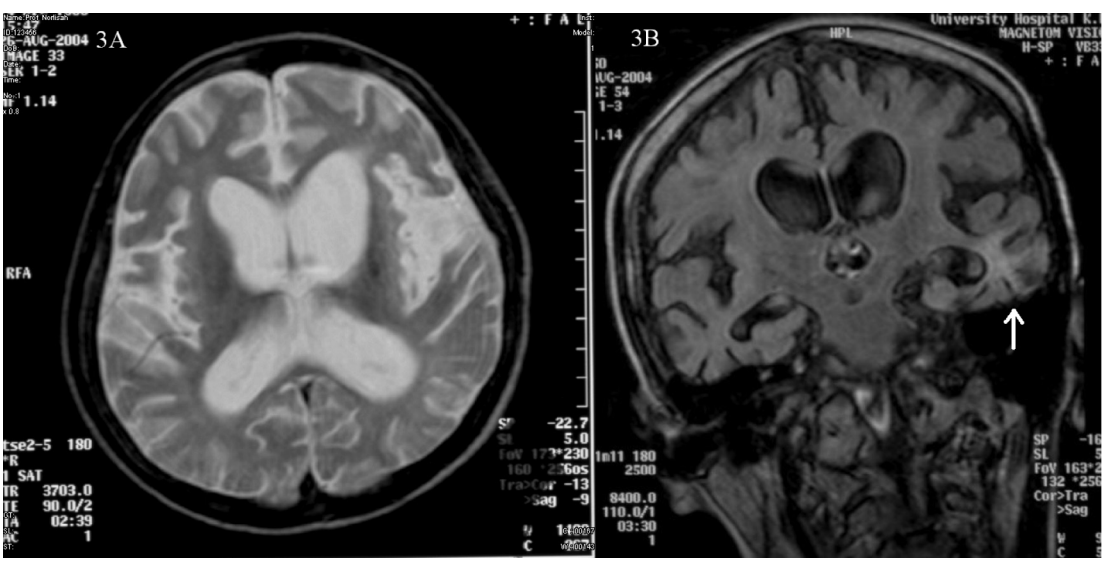

Fig. 3: MRI T2 weighted axial and FLAIR coronal images showing generalized cerebral atrophy with encephalomalacic changes area in previously biopsied area (arrow).

MRI, of the subacute phase, showed bilateral asymmetric involvement of the cortical grey matter and the caudate and putamen region. This could explain the choreiform movement. Interestingly, similar findings have been described in patients with acute measles encephalitis.[2] Pathological studies of patients with SME had documented perivascular mononuclear cell infiltration, white matter demyelination, gliosis and intranuclear and intracytoplasmic eosinophilic inclusions in neuronal and glial cells in the temporal, parietal and occipital cortex[3,5,8-10], as well as in the thalamus[3], consistent with our MRI findings. The delayed MRI showed cerebral atrophy, gliosis and encephalomalacic changes, which coupled with the clinical findings, indicated substantial neuronal loss. The absence of high signal FLAIR and T2W lesions, in contrast to the earlier scan, showed that active inflammation had settled. This is consistent with the stable clinical course.

The importance of host versus viral factor in the pathogenesis of SME is still a subject of debate.[9] Although earlier authors had assumed that cell mediated immunity was important, since most patients were immunosuppressed[3,8], there were reports of SME infection in seemingly immunocompetent patients.[6] Viral isolation study showed that the measles virus isolated from patients with SME were defective in synthesizing normal M protein, suggesting that SME is not a simple opportunistic infection of immunosuppressed host by conventional measles virus, but by a defective virus similar to SSPE.[11] The fact that our patient survived with the cessation of chemotherapy without specific antiviral therapy suggests that the re-institution of cell mediated immunity was sufficient to check further viral propagation and effect viral clearance, as shown by the absence of inflammation in the follow up MRI. This is in support with the hypothesis that host immunity is the determinant factor in the pathogenesis of SME.

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