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Case Report

Progressive multifocal leukoencephalopathy in an adolescent child infected with human immunodeficiency virus: a case report

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ABSTRACT

Progressive multifocal leukoencephalopathy (PML) is an AIDS-defining neurologic disease caused by the JC polyoma virus. It typically occurs in immunocompromised individuals and without treatment, patients have a relentless downhill course. Early detection may improve the prognosis. A 12-year-old male child, a known HIV positive case with abdominal tuberculosis on ATT for 15 days, was brought to us in status epilepticus. After controlling seizures with phenytoin, the child was intubated and mechanically ventilated. Antiretroviral therapy (ART) was withheld temporarily and Anti-tuberculous therapy (ATT) was modified. Plain computerised tomography of the brain showed atrophy of brain parenchyma. Five days after the patient was shifted out of ICU, he again developed multiple episodes of convulsions. All reversible causes were investigated for and ruled out. MRI brain revealed features suggestive of PML with diffuse cerebral and cerebellar atrophy which was disproportionate to age. At present, the incidence of PML in children affected with HIV is still rare. There is still limited information regarding this spectrum of patients, especially their further management following diagnosis. Precise treatment protocols would help guide clinicians in regard to diagnosis and management of these complex cases.

Keywords: Progressive multifocal leukoencephalopathy, Human immunodeficiency virus, Adolescence, Computerized tomography, Magnetic resonance imaging

INTRODUCTION

PML is a severe, demyelinating disease of the central nervous system due to JC Papovavirus infection of the myelin-producing oligodendrocytes.[1,2] The name JC virus is derived from the initials of the index patient. PML typically occurs in immunocompromised individuals, such as patients with congenital HIV infection or other conditions associated with impaired T-cell function.[3] In the course of the infection, extensive myelin breakdown results in white matter destruction. Neurologic symptoms are unspecific and include focal neurological deficits and dementia.[4] Without treatment, patients have a relentless downhill course. The disease is fatal within one year of diagnosis in 90% of patients. Diagnosis can be established by the detection of JC virus DNA in cerebrospinal fluid.[5,6]

Unlike in HIV-infected adults where acute neurologic deterioration secondary to PML is frequent, it is distinctly unusual in HIV-infected children.[7] As a demyelinating disease, PML typically presents with altered mental status, motor deficits and ataxia. Prevalence of JCV specific antibodies increases rapidly during childhood, but the mode of transmission in unknown. PML is rare in HIV-infected children and even more uncommonly associated with immune reconstitution inflammatory syndrome (IRIS) in children.[8] Here, we presented a rare

case of PML occurring in an adolescent infected with HIV.

CASE REPORT

A 12-year-old male child, a known HIV positive case with abdominal tuberculosis on ATT for 15 days, was brought to us in status epilepticus. After controlling seizures with phenytoin, the child was intubated and mechanically ventilated in view of poor GCS and poor respiratory efforts. Adequate ventilatory care, antibiotics, antifungals and other supportive care was given. ART was withheld temporarily and ATT was modified in view of slightly deranged prothrombin time, activated partial thromboplastin time, international normalized ratio and hypoalbuminema. Initial investigations showed pancytopenia, and slightly deranged serum electrolytes which were subsequently corrected. Plain computerized tomography of the brain showed atrophy of brain parenchyma. Cerebrospinal fluid analysis including cytology, microbiology, culture and sensitivity, India ink preparation and CBNAAT was normal. The child had a prolonged ventilator stay of 5 days after which he was extubated. ATT was started and he was shifted out of the ICU to the stepdown ward. However, his sensorium remained depressed.

On probing the past history, the child was diagnosed to be HIV positive at 3 years of age after both his parents were diagnosed with the same. He was on cotrimoxazole prophylaxis since then and on ART since the past five years. The child was apparently doing well until a year back when he was diagnosed with abdominal tuberculosis. He had taken a 6-month course of ATT though the parents noticed deterioration in child's condition since then. Fifteen days before the present admission, child was again diagnosed to have abdominal tuberculosis and ATT was re-started.

Five days after the patient was shifted out, he again developed multiple episodes of convulsions, with more of twitching movements of distal limbs with nodding of head. All reversible causes were investigated for and ruled out. Four more anticonvulsants were added one by one but convulsions persisted and sensorium further deteriorated (GCS 9/15). Subsequently an MRI brain was taken, which showed ill-defined T2/FLAIR hyperintensities in the bilateral periventricular white matter and right superior, middle frontal and right parietal subcortical white matter with no diffusion restriction on DWI or blooming on SWI and no contrast enhancement. There was prominence of the lateral and third ventricles, and prominent basal cisterns and cortical sulci. The features were suggestive of PML with diffuse cerebral and cerebellar atrophy which was disproportionate to age.

DISCUSSION

PML is an AIDS-defining neurologic disease caused by the JC polyoma virus. The majority of humans are infected early in life, and 70% of adults have detectable serum antibodies. The JC virus is a small, simple, DNA virus that establishes long term persistent infection in humans.[9] Primary infection is probably asymptomatic, with persistence of the viruses in the kidney and in B lymphocytes. Although seroconversion to this virus takes place early in life, the nervous system disease only occurs as a reactivation of the infection in conditions associated with T-cell immunodeficiency. The JC virus is believed to be transported to the brain by infected B-lymphocytes, where it then infects the oligodendroglia and alters its ability to make proteins important in producing or maintaining myelin.[7] It is believed to be the result of reactivated latent infection in patients with cell-mediated immunodeficiency or of primary infection in those not previously exposed. CNS infection with the JC virus typically results in multifocal demyelination of the cerebral white matter at the gray-white matter junction, with extension into the deep white matter. Basal ganglia, brain stem and cerebellar lesions have also been described; they are frequently distributed around blood vessels (particularly capillaries) where a dense mononuclear cell infiltrate may be seen. Nuclear inclusions are seen in infected oligodendrocytes at the periphery of demyelinated areas. Bizarre or enlarged astrocytic nuclei with occasional mitotic figures in demyelinated areas had been reported.[10]

Concurrent HIV infection of giant cells in the brain may be seen in patients with PML, but is usually remote from areas of demyelination related to JCV. HIV infection of the brain is known to result in myelin damage and astrocytic gliosis without injury to the oligodendrocyte. Strict neuropathologic criteria allow distinction between HIV and JCV infection even in areas where the infections are concomitant. JCV tropism for oligodendrocytes is an important distinguishing characteristic. When HIV and JCV infection are concurrent, the clinical picture is said to be dominated by PML.[11]

Before the AIDS epidemic, PML was a rare disease, usually developing as a terminal illness in patients suffering from lymphoma and leukemia. It had also been described in patients with sarcoidosis, tuberculosis, carcinomatosis and other disorders as well as in organ transplant recepients.[12] Since the AIDS epidemic, PML has been increasingly recognized, and AIDS appears to be the leading underlying disease predisposing patients to this opportunistic infection. The first case of AIDS-related PML was reported in 1982.[13] PML in HIV-infected children occurs mostly in boys (75%), with a median age of 10 years (range: 7-17 years); our patient was a twelve-year-old male which agreed with these demographics. The geographical distribution of the disease appears to include Brazil, Hungary, India, Japan, South Africa, Thailand and USA. Presenting symptoms include altered speech, hemiplegia, facial palsy and cerebellar dysfunction. This patient presented with acute neurologic deterioration; the differential diagnosis for such an acute course in HIV-infected children will

include meningitis, HIV-related opportunistic infections and neoplasms. Presenting CD4 T-cell counts are usually low, while viral loads are high. The most common outcome is death.[14]

Neuroimaging is an important part of the diagnosis. All patients usually have significant changes on MRI or CT brain. Multiple bilateral areas of white matter demyelination without contrast enhancement or mass effect are typical findings. For CT imaging these appear hypodense, while on MRI they have either decreased or increased signals depending on the imaging parameters.[15] Diffusion-weighted imaging is a new MR imaging technique that had proven its value in evaluating brain tissue injury by quantifying isotropic water diffusion rates. Diffusion tensor imaging is a valuable imaging tool in diseases that affect the microstructural integrity and myelination of the brain as in PML. In HIV-infected children, the most common focal CNS lesion is a primary lymphoma, the imaging characteristics of which include mass effect, oedema and contrast enhancement.[16]

The demyelinating lesions have been seen as confluent regions of abnormal white matter signal throughout the cerebral hemispheres, with posterior fossa involvement in about 10% of cases. Subcortical and periventricular white matter are both usually involved, alone or in combination. The internal and external capsules, corpus callosum and myelinated fibers of the deep gray nuclei may show abnormal signal. Areas of demyelination secondary to JCV have long T1 and T2 relaxation times, no mass effect and rarely show contrast enhancement. When seen, the latter is faint, peripheral and irregular.[15,17]

A confirmed diagnosis of PML requires a compatible clinical syndrome and radiographic findings coupled with brain biopsy demonstrating characteristic pathologic foci of demyelination and oligodendrocytes with enlarged nuclei and basophilic staining intranuclear material. Whether a brain biopsy will yield information that will alter the clinical course of a patient presenting with a demyelinating disease is a clinical judgement. PCR detection of JC virus DNA in CSF provides supportive diagnostic information in the presence of a compatible clinical syndrome and radiographic findings, and can be used for diagnosis when a brain biopsy is not feasible.[9]

With continued improvements in medical therapy for children with HIV infection, the average life expectancy for children with perinatally acquired HIV infection has risen to more than 8 years. Treatment for PML is based on HAART initiation or optimization, which has shown improved mortality associated with lower HIV RNA plasma viral levels and higher CD4 T-cell count. No effective therapy for JC virus exists. Randomized clinical trials have evaluated vidarabine and cidofovir; neither is effective in producing clinical improvement and neither is recommended.[18] When ART is initiated and CD4+ T lymphocyte counts rise, certain patients will experience neurologic improvement and others might become neurologically stable. However, reports have documented patients experiencing worse neurologic manifestations after initiation of ART. In certain instances, this worsening is caused by an immune reconstitution inflammatory syndrome; other cases represent the natural history of PML. No role exists for antiviral agents in the prevention of recurrence or progression of PML.[19]

CONCLUSION

At present, the incidence of PML in children affected with HIV is still rare. As survival rates of children with HIV increase, an increase in the incidence may be expected, thus making it essential to include JC virus infection in the differential diagnosis of children with acute neurologic deterioration. There is still limited information regarding this spectrum of patients, especially their further management following diagnosis. Precise treatment protocols would help guide clinicians in regard to diagnosis and management of these complex cases.

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