

## Progressive Multifocal Leukoencephalopathy as the Initial Presentation in an Apparently Healthy Child

Dear Sir,

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disorder of central nervous system caused by reactivation of JC polyomavirus in immune-suppressed states. It is usually seen in individuals with HIV infection, hematological malignancies, post-transplant recipients, and secondary to use of immunomodulators drugs.<sup>[1]</sup> PML is extremely rare in children due to the low seroprevalence of JC virus in the young.<sup>[2]</sup> Usually, it is seen in children with diagnosed HIV infection.<sup>[3]</sup> We report a rare occurrence of PML as the presenting feature of HIV infection in a child. A 10-year-old previously normal boy presented with a history of horizontal double vision on looking toward right since 1 month. A week later, he developed difficulty in walking with frequent falls and weakness in right upper limb. His parents also reported poor concentration, hyperactivity, and decline in school performance. There was no history of seizures, vision or hearing impairment, abnormal movements, sensory loss, and bladder or bowel involvement. There was no preceding history of fever, headache, vomiting, rash, or head trauma. He had been adopted at 3 months of age. The birth and perinatal details were unknown. His biological mother had expired 1 month after delivering the child. His developmental milestones had been age appropriate and was apparently well till the current illness.

Examination revealed an alert, thin built boy, with stable vitals and weight 18 Kg (<-3 SD), height 120 cm (<-3 SD), and BMI 12.5 (<-3 SD). Neurological examination revealed reduced attention span but preserved recent and remote memory with cerebellar dysarthria. He had right lateral rectus palsy

with normal fundus examination. His gait was ataxic with hypotonia of all four limbs. Cerebellar signs were positive bilaterally (right > left). Rest of the examination revealed no abnormalities.

Investigations showed normal hemogram and routine biochemical profile. MRI brain revealed ill-defined asymmetric hyperintense signal changes involving the medial aspect of bilateral cerebellar hemispheres (right > left), vermis, and middle cerebellar peduncles without mass effect or contrast enhancement [Figure 1]. Based on the MRI findings, the possibilities of inflammatory demyelination or PML were considered. CSF study showed normal cells and protein with absence of oligoclonal bands. The serology for anti-neuromyelitis optica (NMO) aquaporin 4 and anti-myelin oligodendrocyte glycoprotein (MOG) antibody was negative. The HIV antibody test was reactive with HIV Virus RNA level of 64365 copies/mL and CD4 T cell count of 28 cells/ $\mu$ L (ref range: 423–1724 cells/ $\mu$ L). Parental HIV testing was nonreactive. The CSF tested positive for JC virus by PCR testing. A detailed review for risk factors did not reveal any history of unsafe injections, intravenous drug abuse, blood transfusions, or sexual abuse.

The child was diagnosed as having HIV infection with acquired immunodeficiency syndrome (AIDS) with PML. He was started on highly active antiretroviral therapy (HAART) along with supportive care. He continued to worsen after starting HAART with deteriorating gait, speech, and swallowing difficulties and ultimately became nonambulatory over next 6 weeks. In view of the



**Figure 1:** Magnetic resonance imaging of the brain of child with progressive multifocal leukoencephalopathy (PML). T2 FLAIR axial section shows ill-defined hyperintense signals involving medial aspect of bilateral cerebellar hemisphere (right > left), vermis, and bilateral middle cerebellar peduncle (right > left) without mass effect

clinical worsening, a possibility of immune reconstitution inflammatory syndrome (IRIS) was considered. However, the repeat CD4 counts were found to be low (35 cells/ $\mu$ L). Repeat MRI showed progression of the cerebellar lesion extending into the brainstem without contrast enhancement. Hence, the progression of disease was confirmed and he was continued on HAART with supportive care without steroids. On follow-up after 6 months, child showed mild improvement; he was able to recognize parents, chew and swallow food, able to sit with support. CD4 count was still low (37 cells/ $\mu$ L). He continues to be in follow-up.

PML is an AIDS-defining condition in children infected with HIV. Reactivation of the latent JC polyomavirus causes selective destruction of oligodendrocytes leading to the progressive demyelination of the central nervous system. About 3%–4% of adults with HIV are affected by the PML, with 50% mortality in the affected patients.<sup>[4]</sup> HIV/AIDS is the most common risk factor for PML. In children, only 31 cases of PML have been reported so far, out of which two-third cases are secondary to HIV infection.<sup>[3,5]</sup>

The clinical features of PML include limb paresis, speech abnormality, ataxia, cognitive deficits, and ophthalmoparesis; seizures are rare.<sup>[4]</sup> Radiologically, there are single or multifocal white matter lesions which affect the parieto-occipital white matter, corpus callosum, cerebellar hemisphere, middle cerebellar peduncles, and brainstem with sparing of periventricular white matter. Basal ganglia involvement is seen in up to 50% of patients. Spinal cord and optic nerve involvement is extremely rare in PML and usually points toward immune-mediated demyelination. Classically, there is no mass effect or contrast enhancement; however, contrast enhancement can occur with immune reconstitution on HAART therapy.<sup>[6]</sup> Our case had isolated cerebellar lesion which was more favorable of PML than acute demyelination.

The diagnosis was confirmed by the presence of JC virus DNA in CSF.<sup>[1]</sup>

In most pediatric PML cases associated with HIV, the children already have diagnosed HIV/AIDS. PML occurring as the presenting feature of HIV has only been reported in 4 children till date.<sup>[5,7-9]</sup> Similar to our case, all these four children had been apparently healthy and presented with subacute onset of limb paresis. All these four had documented perinatal transmission. The CD4 count in all of these children was extremely low (<20 cells/ $\mu$ L) except one. Three out of these four died, and no information was available for the fourth.<sup>[5]</sup>

In our patient too, the likely mode of HIV acquisition was perinatal. He was apparently healthy till presentation without any history of prior hospital admissions, recurrent OPD visits for minor ailments or any chronic disease prior to this. However, he had severe malnutrition at outset with no other clinical pointers of HIV/AIDS, hence, was not suspected for the same at the outset.

PML is a devastating disease with no specific treatment except the restoration of cell-mediated immunity by antiretroviral therapy. Recent study in adults has reported one-year survival of 60% in HIV associated PML.<sup>[10]</sup> However, in children, only 25% survival has been reported with significant sequelae.<sup>[3]</sup> Our patient case showed initial clinical deterioration due to disease progression and later stabilization might be due to HAART therapy and supportive care. To conclude, PML must be considered as a strong differential in presence of any subacute focal neurological deficit with characteristic neuroimaging abnormality even when the child appears apparently healthy.

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### Conflicts of interest

There are no conflicts of interest.

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