

## A Rare Case of Progressive Multifocal Leukoencephalopathy

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### Abstract :

*Progressive Multifocal Leukoencephalopathy is a deadly demyelinating disease of the Central Nervous System due to lytic infection of oligodendrocytes by the ubiquitous opportunistic polyoma virus John Cunningham Virus (JC Virus). Although 70% of the general adult population have antibodies to John Cunningham virus (IgG), indicative of prior infection, less than 10% of healthy adults show evidence of ongoing viral replication. Reactivation of latent John Cunningham Virus occurs as a result of advancing immune depletion. It is seen in approximately 4% of patients with Acquired Immune Deficiency Syndrome. These patients usually present with multifocal neurological deficits. Presenting a patient of this fatal disease who was diagnosed on radiological imaging modality.*

**Key Words :** JC Virus, HIV, Seizures

### Introduction :

Clinical disease of the nervous system accounts for a significant degree of morbidity in a high percentage of patients with Human Immune Deficiency Virus (HIV) infection. Neurologic problems in HIV-infected may be primary to the pathogenic processes of HIV infection or secondary to opportunistic infections or neoplasms. Secondary diseases of the CNS occur in approximately 33% AIDS patients. Frequency is considerably less in patients receiving effective Anti-Retroviral drugs. Neurologic problems directly attributable to HIV occur throughout the course of infection & may be inflammatory, demyelinating, or degenerative. Virtually all patients with HIV infection have some degree of nervous system involvement with the virus. Neurologic diseases are classified as Opportunistic Infections, Neoplasms, Myelopathies, Neuropathies & results of HIV infection itself.

### Case:

A 34 year old male presented with recurrent generalized tonic-clonic convulsions accompanied by tongue-bite, sphincter incontinence & post-ictal

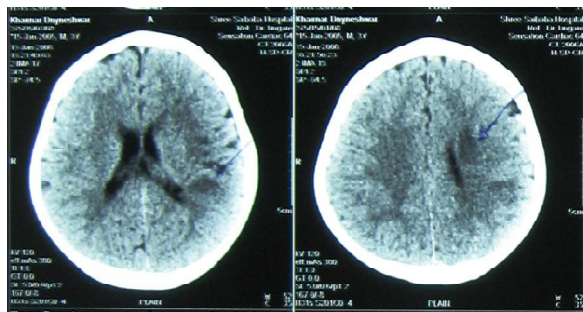
confusion. He was known to be immunocompromised (HIV positive) with history of abdominal Tuberculosis in the form of lymphadenopathy & had completed treatment under DOTS. He had also received Anti-retroviral Therapy (ART) for 4 months but discontinued it against medical advice.

On examination, he was comatose, vitals were stable and chest was clear. He was moving all 4 limbs. Pupils were bilaterally equal & reacting to light. Cranial nerves were normal. Plantar response was extensor bilaterally & there were no signs of meningeal irritation.

He was hospitalized in the General ward & stabilized with anti-convulsants, anti-cerebral oedema measures & other supportive therapy.

Over the next 2 days, seizures stopped but he remained comatose. Cerebrospinal fluid (CSF) examination was performed which was normal. A Computed Tomography Scan of the head was performed (Fig. 1) which showed bilateral, symmetrical non-enhancing hypodense white matter lesions (more prominent in frontal & white-matter regions) with mild generalized cerebral atrophy, suggestive of Progressive Multifocal Leukoencephalopathy.

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**Figure 1:** Bilateral, symmetrical non- enhancing hypodense white matter lesions (more prominent in frontal regions) with mild generalized cerebral atrophy suggestive of Progressive Multifocal Leukoencephalopathy.

### Discussion:

*John Cunningham Virus* (JC Virus), a human polyoma virus which is the etiologic agent of Progressive **Multifocal Leukoencephalopathy** (PML), is an important opportunistic pathogen<sup>[1]</sup> in patients with AIDS. While ~70% of the general adult population have antibodies to JC virus, indicative of prior infection, <10% of healthy adults show evidence of ongoing viral replication<sup>[2]</sup>.

PML was described as early as 1930 by the German neuropathologist *Hallervorden*<sup>3</sup>. It was first clearly delineated as a syndrome in 1958 by *Astrom et al*<sup>3</sup>. *ZuRhein*<sup>[3]</sup> proposed that a polyoma virus was responsible on the basis of electron microscopic criteria & it was confirmed by the isolation of a papovavirus, JC virus, in human brain cultures in 1971. It was characterized on the basis of 3 cardinal histopathologic features<sup>[3]</sup>:

- Multifocal Demyelination
- Hyperchromatic enlarged nuclei of oligodendrocytes
- Enlarged bizarre astrocytes with lobulated hyperchromatic nuclei

*John Cunningham Virus* (JC Virus) was named after the initials of the first afflicted patient from whose brain the agent was recovered & it infects oligodendrocytes causing lysis through 5-HT<sub>2A</sub> serotonin receptor<sup>[3]</sup>.

Most persons acquire this virus at a young age. The site of initial viral entry involves the tonsils & it

remains latent in the kidneys & lymphoid tissues for life after primary infection<sup>[3]</sup>. Reactivation of the virus results in the presence of circulating infected lymphocytes those are capable of crossing the blood-brain barrier & passing infection to astrocytes at the border of vessels. Infection is then augmented through multiplication & eventual infection of adjacent oligodendrocytes. A specific deficiency in cellular immune response to JCV antigen is superimposed on generalized cellular immunodeficiency - Leukocyte migration inhibitory factor. Reactivation of latent JC virus occurs as a result of advancing immune depletion (defective cell- mediated immunity)

- Haematologic malignancies
- Acquired Immunodeficiency Disease Syndrome (AIDS)
- Other immunosuppressive states
- Chronic debilitating diseases

JC Virus belongs to the Polyomavirus genus in the Papovaviridae family & is a double-stranded DNA-containing virus with an icosahedral symmetry.

PML is the only known clinical manifestation of JC virus infection. It is a late manifestation of AIDS & is seen in ~4% of patients with AIDS. The lesions of PML<sup>[5]</sup> begin as small foci of demyelination in subcortical white matter that eventually coalesce. The cerebral hemispheres, cerebellum & brainstem may all be involved. Occasionally spinal cord can be involved.

The lesions are patches of irregular ill-defined destruction of the white matter ranging in size from millimetres to extensive involvement of an entire lobe of the brain<sup>[6,7]</sup>. The patch of demyelination is most often sub- cortical. There are scattered lipid- laden macrophages & reduced number of axons in the centre with enlarged oligodendrocyte nuclei whose chromatin is replaced by glassy amphophilic viral inclusion at the edge accompanied by giant astrocytes with irregular, hyperchromatic multiple nuclei<sup>[6,7]</sup>.

Patients typically have a protracted course with multifocal neurological deficits, with or without changes in mental status<sup>[3]</sup>. Approximately, 20% of patients experience seizures. Ataxia, hemiparesis, visual field defects, aphasia, headaches & sensory defects may occur. Causes of seizures in HIV as estimated by various authors<sup>[8]</sup> are HIV Encephalopathy in 24-47%

patients, Cerebral Toxoplasmosis in 28%, Cryptococcal Meningitis in 13%, Primary Central Nervous System Lymphomas in 4% & PML in 1% patients. Magnetic Resonance Imaging (MRI) is more revealing than Computed Tomography (CT) & it typically reveals multiple, non-enhancing white matter lesions that may coalesce & have a predilection for the occipital & parietal lobes. The lesions show signal hyperintensity on T2-weighted images & diminished signal on T1-weighted images. The measurement of JC virus DNA levels in Cerebrospinal Fluid has a diagnostic sensitivity of 76% & a specificity of close to 100%. Prior to the availability of potent HAART (Highly Active Antiretroviral Therapy) combination therapy, the majority of patients with PML died within 3-6 months of onset of symptoms. Paradoxical worsening of PML has been seen with initiation of HAART as an immune reconstitution syndrome<sup>[9]</sup>. There is no specific treatment for PML; however a minimal median survival of 18 months & survival of >7 years have been reported in patients with PML treated with HAART. Unfortunately, only ~50% of patients show neurologic improvement with HAART. Studies with other antiviral agents<sup>9</sup> have failed to show clear benefit. Factors influencing a favorable prognosis for PML in the setting of HIV infection include a CD4+ T cell count >100/ $\mu$ l at baseline & the ability to maintain an HIV viral load of <500 copies per ml. Baseline HIV-1 viral load does not have independent predictive value of survival. PML is one of the few opportunistic infections that continues to occur with same frequency despite the widespread use of ART.

### Conclusion:

It was concluded that this patient had PML on the basis of characteristic radiological findings keeping in view the clinical presentation. We could not perform CSF testing for JC Virus antigen owing to lack of this facility in the vicinity of our Institute. An MRI scan of the brain would have demonstrated the lesions better.

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