Progressive multifocal leuкоencephalopathy (PML) is an uncommon demyelinating disease of the central nervous system caused by targeted oligodendroglial destruction by JC virus, a common, asymptomatic childhood infection that persists throughout life in latent form, affecting up to 80% of adults. The virus can be reactivated later in life in cases of immune deficiency such as AIDS, caused by HIV-1 infection. PML can be present in up to 5% of AIDS patients, causing considerable morbidity and rapid progression to death within a few months. Recently, highly active antiretroviral therapy (HAART) and other forms of antiviral treatment have been shown to increase survival in these patients.

Clinical manifestations are caused by progressive white matter destruction and vary with lesion location. Symptoms consist of focal motor and sensory deficits, gait abnormalities, speech and language disturbances, headache, and vision deficit, although dementia, seizures, and movement disorders have also been described. On magnetic resonance imaging (MRI), lesions are characteristically T1 hypointense with high proton density and T2 signal intensity, without mass effect or contrast enhancement, and are preferentially located in the subcortical white matter, mostly in the parieto-occipital region.

Diagnosis of PML is typically based on MRI findings in the appropriate clinical setting. Confirmation of JC virus infection requires polymerase chain reaction (PCR) amplification of viral DNA from cerebrospinal fluid or in situ hybridisation (ISH) of pathology specimens with JC virus DNA probes which mark inclusion bodies in oligodendrocyte nuclei.

A case of progressive multifocal leuкоencephalopathy in an AIDS patient is described, which evolved over a 13 month period. The ataxia persisted as the only clinical finding for several months before the appearance of a severe tetraparesis and cachexia. Throughout the clinical progression, magnetic resonance imaging (MRI) revealed the presence of bilateral, progressive, isolated, and symmetrical lesions involving the red nuclei, subthalami, thalami, lenticular nuclei, and primary motor cortices. Neuropathological examination, supplemented by in situ hybridisation for JC virus DNA, confirmed that the lesions were those of progressive multifocal leuкоencephalopathy (PML). The exceptional clinical presentation of PML in this case is the first report of progressive multifocal leuкоencephalopathy caused by PML. The selective nature of the lesions confirms the role of the dentato-rubral-thalamo-cortical tract in the pathogenesis of progressive multifocal leuкоencephalopathy. The atypical MRI findings further emphasise the need for expanded diagnostic criteria for PML in AIDS patients and support the use of more aggressive diagnostic methods as new treatments become available.

CASE REPORT

The patient was a 36 year old white man, a former intravenous drug user known to be infected with HIV-1 and hepatitis C virus since 1991, and was on treatment with zidovudine. There were no opportunistic infections up to 1997, and his last viral count was 27 330 cp/ml (CD4 cell count, 45 cells/µl).

In April 1997 he insidiously developed gait ataxia and intention tremor in the upper limbs. Three months later he was admitted because of increased severity of the ataxia and the appearance of action and stimulus sensitive myoclonus. Brain MRI revealed isolated bilateral T2 hyperintense lesions in the thalami without gadolinium enhancement or mass effect. He was started on HAART, clonazepam, and later valproate, with little effect on the myoclonus or the ataxia.

In October 1997 he was admitted to our institution for evaluation. He had a severe cerebellar syndrome, including gait and limb ataxia, decreased muscular tone, and scanning dysarthria, together with abundant, generalised, and irregular action and stimulus sensitive myoclonus. General physical and neurological examination was otherwise unremarkable. Brain MRI showed an increase in size of the thalamic lesions, which extended to the mesencephalon and red nuclei, and the presence of similar, faint, hyperintense subcortical lesions delineating the motor cortex bilaterally (fig 1, A and B).

Laboratory testing revealed a slight macrocytic anaemia with normal vitamin B-12 and folate (attributed to HAART marrow toxicity). CSF cytological analysis and microbiological examination were normal; CSF viral serologies were negative for EBV, CMV, HSV, VZV, HTLV I and II, measles, influenza, parainfluenza, and adenoviruses. On viral serology he was found to be IgG positive for measles, HSV, CMV, EBV, and VZV. Blood tests for Lyme borreliosis, Bartonella and Listeria spp, HTLV I and II, and VDRL were negative. Serum and CSF lactate and pyruvate were normal. Anti-Hu, anti-Yo, anti-Ri, and vasculitic antibodies (ANA, ANCA, and ENA) were not detectable. An EEG showed a diffuse increase in slow activity, with no evidence of cortical spikes. Motor evoked potentials revealed decreased excitability of the motor cortex, with normal central conduction time. A trial of isoniazid was without apparent benefit on the cerebellar tremor. Treatment with HAART, valproate (1 g/day), and clonazepam (8 mg/day) was maintained.

During the following months the patient developed a symmetrical spastic tetraparesis, together with deterioration in his general physical condition. In February 1998, HAART was stopped because of aplastic anaemia (viral load 905 cp/ml; CD4 count, 90 cells/µl). By then he was wheelchair bound, tetraplegic, anarthric, and had severe dysphagia. He appeared still to be able to understand simple sentences but was unable to communicate. Brain MRI at this time showed T2 and FLAIR hyperintense lesions involving the primary motor cortices bilaterally and the adjacent cerebral white matter; the thalami, lenticular nuclei, subthalamic region, and the crus cerebri in the red nucleus region were also affected (fig 1, C–F).

In subsequent months he was again admitted with a respiratory infection and severe cachexia, became comatose, and...
eventually died from *Pseudomonas aeruginosa* pneumonia. His last viral count was 124 310 cp/ml, with 14 CD4 cells/µl.

A necropsy examination of the brain was performed. Mac- 
roscopically the encephalon showed numerous foci of 
grey-yellow discoulouration and softening, mainly in the 
cerebral hemispheric and cerebellar white matter, and small 
cavitations in the basal ganglia bilaterally (fig 2A). Histologi-
cal staining showed abundant demyelinating lesions in the 
grey and white matter. The white matter lesions consisted of 
large confluent areas of myelin loss together with a scant 
perivascular mononuclear and macrophagic infiltrate, includ-
ing numerous reactive astrocytes, myelin debris filled macro-
phages, and oligodendrocytes with nuclear inclusions of 
ground glass appearance (fig 2B). In the grey matter there 
were small and medium sized demyelinating foci extending 
from the subjacent gyral white matter into the deep cortical 
layers. Neurones were of normal morphology and density, and 
there were no specific findings attributable to HIV infection in 
either grey or white matter.

Lesions in the brain were extensive, affecting the hemi-
spheric white matter of all lobes but mainly the frontal and 
parietal periplandic regions, followed in severity by the tem-
poral and occipital lobes. The fornix and corpus callosum were 
comparatively less affected. The basal ganglia were extensively 
involved, particularly on the right, including areas of 
cavitation in the external capsule, thalamus, and lenticular 
nucleus, with relative sparing of the caudate nucleus and 
internal capsule. In the mesencephalon these lesions were 
small and dispersed, involving both pyramidal and Reil tracts, 
locus niger, and red nuclei. The pons and medulla had fewer

![Figure 1](brain_mri.jpg) **Figure 1** Brain magnetic resonance imaging (MRI), 1.5 Tesla: axial and coronal T1 and T2 weighted imaging. (A) and (B): MRI scan at six months; (C) to (F): MRI scan at 11 months.

![Figure 2](brain_necropsy.jpg) **Figure 2** Brain necropsy. (A) Coronal section of the basal ganglia showing demyelinating lesions and cavitation in the right thalamus (Luxol fast blue stain). (B) Photomicrograph of demyelinating lesion showing reactive astrocytes, macrophages, and oligodendrogial nuclear inclusions (luxol fast blue ×400). (C) In situ hybridisation for JC virus, with positive oligodendrogial nuclei (×300).
lesions, affecting mainly the olivary nuclei and the trapezoid bodies. The cerebellum showed similar small foci in the deep white matter and dentate nuclei; the folia were completely normal, with preservation of both granular and Purkinje cell layers. The inferior and superior cerebellar peduncles were also affected.

An immunohistochemical assay with anti-JC virus antibod-
ies was positive in these lesions, as was in situ hybridisation for JC virus DNA, showing the presence of positive oligodendrocytic nuclei (fig 2C); these findings confirmed the diagnosis of progressive multifocal leucoencephalopathy (PML).

**DISCUSSION**

This PML case raises three points for discussion. The first is the exceptional clinical presentation of the disease in this patient, consisting of a myoclonic ataxia which was the sole neurological manifestation of PML for several months. Move-
ment disorders are relatively common in AIDS, affecting up to 11% of patients, and can be the first manifestation of the disease. However, Antiviral treatment with interferon or cidofovir extended survival; PML progression was not affected, our patient there was a documented decrease in viral load and parkinsonism, movement disorder, with a reported incidence of only 11% of patients, and can be the first manifestation of the disease. Hemiballismus-hemichorea is by far the commonest disorder reported, usually caused by a toxoplasmic abscess of the basal ganglia. however, is rarely the cause of a movement disorder, with a reported incidence of only 0–2.6%, which reflects the preferential involvement of white matter in the parietal and occipital areas. Basal ganglia involvement, when it occurs, is mostly related to the white matter tracts coursing through these structures, manifesting itself as motor or sensory dysfunction. Some cases, however, have been related to white matter demyelination, even in cases with atypical findings such as predominant grey matter involvement. The appearance of new, more specific treatment options will require that the diagnosis of PML be pursued more aggressively, through PCR confirmation of JC virus infection and brain biopsy when feasible, so that treatment may be instituted earlier.

The progressive myoclonic ataxias are a heterogeneous group of rare conditions causing the clinical triad of progressive ataxia and severe myoclonus, mild epilepsy, and cognitive changes. Possible aetiologies are mitochondrial encephalomyopathies, storage disorders, some progressive neurodegenerative diseases, paraneoplastic syndromes, transmissible spongiform encephalopathies, viral encephalitis, and, recently, coeliac disease. To our knowledge, ours is the first description of a progressive myoclonic ataxia caused by PML. Although there have been few clinicalpathological studies of progressive myoclonic ataxia to date, all seem to point to preferential involvement of regulatory neocerebellar pathways between the cerebellum, red nucleus, thalamus, and motor cortex. In our case, we believe that the initial selective involvement of structures in the dentato-rubo-thalamo-cortical pathway, as documented by serial MRI, was responsible for the progressive ataxia. Later on, the extension of the lesions primarily to the motor cortices and underlying white matter led to motor paralyzes and to deterioration in the patient's general clinical condition. The abundance of lesions in the motor cortex and brain stem makes it difficult to attribute the myoclonus to any particular origin, but the concomitant appearance of the myoclonus with MRI documentation of subcortical demyelinating points to a cortical origin, as in a recent report. Prolonged survival in PML has become more common since the introduction of HAART. Similarly, in our patient there was a documented decrease in viral load and extended survival; PML progression was not affected, however. Antiviral treatment with interferon or cidofovir might have been more effective in that respect.

Secondly, unlike the usual presentation for PML, only the thalamus were initially affected in this case. Although grey matter involvement in PML has been reported in various studies, it is usually considered to be a secondary phenomenon related to white matter destruction. Some cases, however, have been reported with predominantly grey matter disease in the cerebral and cerebellar cortices, or in the basal ganglia; in these, as in our case, the clinical picture has differed from the usual one, consisting of dementia, akinetic-rigid parkinsonism, progressive cerebellar syndrome, myoclonus and athetosis, and motor dyspraxia. The localisation of the pathological process to grey matter structures is a probable explanation for these aberrant clinical presentations and supports the proposed designation of JC virus encephalitis for these cases. There is presently no explanation for the selectivity of the process to the grey matter in the context of generalised JC virus infection. It is conceivable that different strains of JC virus could be involved, as well as host factors such as differences in the immune response or viral receptor subtypes.

Finally, MRI diagnostic criteria for PML should also be reconsidered. Atypical imaging findings in this disease have become increasingly more common in recent years, especially in AIDS patients. Contrast enhancement, early grey matter involvement, and cases with normal MRI have all been reported. In our case the early involvement of the deep grey matter and the anatomical selectivity of the lesions on MRI were the main obstacles to the diagnosis of PML, which was only confirmed after pathological examination of the brain. Cases such as ours support the creation of revised and expanded imaging criteria for PML, particularly in AIDS patients.

The increasing spectrum of clinical and imaging findings being reported in the literature requires that PML enter the differential diagnostic list for all HIV positive patients with aberrant clinical presentations and MRI findings compatible with demyelination, even in cases with atypical findings such as predominant grey matter involvement. The appearance of new, more specific treatment options will require that the diagnosis of PML be pursued more aggressively, through PCR confirmation of JC virus infection and brain biopsy when feasible, so that treatment may be instituted earlier.

**ACKNOWLEDGEMENTS**

We thank Drs Isabel Cravo and Pedro Evangelista, of the neuroradiology department of the Hospital Egas Moniz, for their critical revaluation of all the MRI images.

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Received 2 August 2001

Accepted 10 January 2002

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J Neurol Neurosurg Psychiatry 2002 72: 653-656
doi: 10.1136/jnnp.72.5.653

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