

## SHORT REPORT

## Progressive myoclonic ataxia and JC virus encephalitis in an AIDS patient

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A case of progressive myoclonic ataxia 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 leucoencephalopathy (PML). The exceptional clinical presentation of PML in this case is the first report of progressive myoclonic ataxia caused by PML. The selective nature of the lesions confirms the role of the dentato-rubral-thalamo-cortical tract in the pathogenesis of progressive myoclonic ataxia. 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.

Progressive multifocal leucoencephalopathy (PML) is an uncommon demyelinating disease of the central nervous system caused by targeted oligodendroglial destruction by JC virus,<sup>1–3</sup> a common, asymptomatic childhood infection that persists throughout life in latent form, affecting up to 80% of adults.<sup>4–6</sup> The virus can be reactivated later in life in cases of immune deficiency such as AIDS, caused by HIV-1 infection.<sup>3, 4, 6–8</sup> PML can be present in up to 5% of AIDS patients, causing considerable morbidity and rapid progression to death within a few months.<sup>3, 6, 8, 9</sup> Recently, highly active antiretroviral therapy (HAART) and other forms of antiviral treatment have been shown to increase survival in these patients.<sup>9–11</sup>

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.<sup>3–5, 7, 8, 12, 13</sup> 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.<sup>7, 14, 15</sup>

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.<sup>3, 4, 6, 8, 15</sup>

## 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/ $\mu$ l).

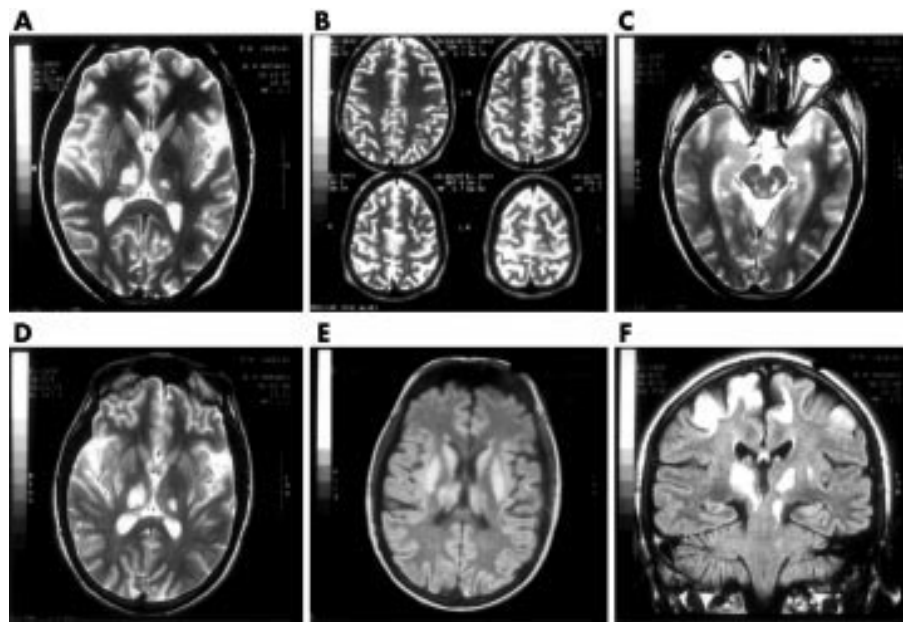
In April 1997 he insidiously developed gait ataxia and intention tremor in the upper limbs. Three months later he was admitted because of increased severity of the ataxia and the appearance of action and stimulus sensitive myoclonus. Brain MRI revealed isolated bilateral T2 hyperintense lesions in the 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 cytochemical 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/ $\mu$ l). 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



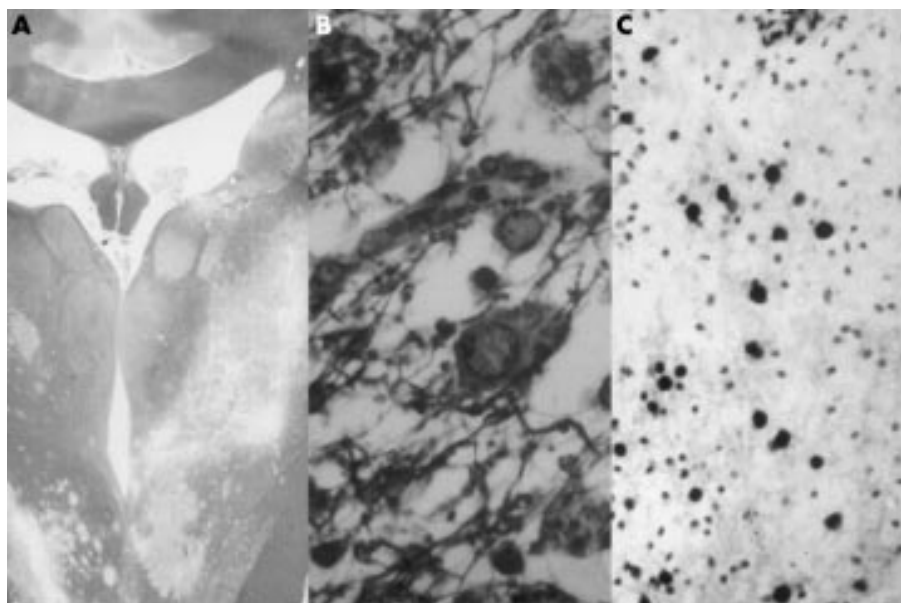
**Figure 1** Brain magnetic resonance imaging (MRI), 1.5 Tesla: axial and coronal T1 and T2 weighted imaging. (A) and (B): MRI scan at six months; (C) to (F): MRI scan at 11 months.

eventually died from *Pseudomonas aeruginosa* pneumonia. His last viral count was 124 310 cp/ml, with 14 CD4 cells/ $\mu$ l.

A necropsy examination of the brain was performed. Macroscopically the encephalon showed numerous foci of grey-yellow discoloration and softening, mainly in the cerebral hemispheric and cerebellar white matter, and small cavitations in the basal ganglia bilaterally (fig 2A). Histological 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, including numerous reactive astrocytes, myelin debris filled macrophages, 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 hemispheric white matter of all lobes but mainly the frontal and parietal perirolandic regions, followed in severity by the temporal 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 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 oligodendroglial nuclear inclusions (Luxol fast blue  $\times 400$ ). (C) In situ hybridisation for JC virus, with positive oligodendroglial nuclei ( $\times 300$ ).

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 antibodies 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. Movement disorders are relatively common in AIDS, affecting up to 11% of patients, and can be the first manifestation of the disease.<sup>16-18</sup> Hemiballismus-hemichorea is by far the commonest disorder reported, usually caused by a toxoplasmic abscess of the basal ganglia.<sup>16-17</sup> PML, however, is rarely the cause of a movement disorder, with a reported incidence of only 0-2.6%,<sup>11</sup> 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.<sup>8-9</sup>

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.<sup>19-21</sup> Possible aetiologies are mitochondrial encephalomyopathies, storage disorders, some progressive neurodegenerative diseases, paraneoplastic syndromes, transmissible spongiform encephalopathies, viral encephalitis, and, recently, coeliac disease.<sup>19-21</sup> To our knowledge, ours is the first description of a progressive myoclonic ataxia caused by PML. Although there have been few clinicopathological 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.<sup>19-21</sup> In our case, we believe that the initial selective involvement of structures in the dentato-rubro-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 paralysis 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 demyelination points to a cortical origin, as in a recent report.<sup>21</sup> Prolonged survival in PML has become more common since the introduction of HAART.<sup>9</sup> 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.<sup>10-11</sup>

Secondly, unlike the usual presentation for PML, only the thalami 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.<sup>8</sup> 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,<sup>5</sup> akinetic-rigid parkinsonism,<sup>12</sup> progressive cerebellar syndrome,<sup>8</sup> myoclonus and athetosis,<sup>8</sup> and motor dyspraxia.<sup>13</sup> 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.<sup>8</sup> 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.<sup>22</sup>

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,<sup>4-12-23</sup> early grey matter involvement,<sup>4-8-12-13</sup> and cases with normal MRI<sup>13</sup> 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 newer, 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.

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## REFERENCES

- Zu Rhein GM**. Association of papova-virions with a human demyelinating disease (progressive multifocal leucoencephalopathy). *Prog Med Virol* 1969;11:185-247.
- Narayan O**, Penney JB, Johnson RT, *et al*. Etiology of progressive multifocal leucoencephalopathy. Identification of papovavirus. *N Engl J Med* 1973;289:1278-82.
- Berger JR**, Pall L, Lanska D, *et al*. Progressive multifocal leucoencephalopathy in patients with HIV infection. *J Neuroviral* 1998;4:59-68.
- Rosas MJ**, Simões-Ribeiro F, An SF, *et al*. Progressive multifocal leucoencephalopathy: unusual MRI findings and prolonged survival in a pregnant woman. *Neurology* 1999;52:657-9.
- Zunt JR**, Tu RK, Anderson DM, *et al*. Progressive multifocal leucoencephalopathy presenting as human immunodeficiency virus type 1 (HIV)-associated dementia. *Neurology* 1997;49:263-5.
- Greenlee JE**. Progressive multifocal leucoencephalopathy. In: Aminoff MJ, Goetz CG, eds. *Handbook of clinical neurology, vol 27: Systemic diseases, part III*. Amsterdam: Elsevier, 1998:399-430.
- Lizerbram EK**, Hesselink JR. Viral infections. *Neuroimaging Clin North Am* 1997;7:261-80.
- Sweeney BJ**, Manji H, Miller RF, *et al*. Cortical and subcortical JC virus infection: two unusual cases of AIDS associated progressive multifocal leucoencephalopathy. *J Neurol Neurosurg Psychiatry* 1994;57:994-7.
- Clifford DB**, Yiannoutsos C, Glicksman MS, *et al*. HAART improves prognosis in HIV-associated progressive multifocal leucoencephalopathy. *Neurology* 1999;52:623-5.

- 10 **De Luca A**, Giancola ML, Ammassari A, *et al*. Potent anti-retroviral therapy with or without didanosine for AIDS-associated progressive multifocal leukoencephalopathy: extended follow-up of an observational study. *J Neuroviral* 2001;**7**:364–8.
- 11 **Geschwind M**, Skolasky R, Royal W, *et al*. The relative contributions of HAART and alpha-interferon for therapy of progressive multifocal leukoencephalopathy in AIDS. *J Neuroviral* 2001;**7**:353–7.
- 12 **Singer C**, Berger JR, Bowen BC, *et al*. Akinetic-rigid syndrome in a 13-year-old girl with HIV-related progressive multifocal leukoencephalopathy. *Mov Disord* 1993;**8**:113–16.
- 13 **de Toffol B**, Vidailhet M, Gray F, *et al*. Isolated motor control dysfunction related to progressive multifocal leukoencephalopathy during AIDS with normal MRI. *Neurology* 1994;**44**:2352–5.
- 14 **Whiteman ML**, Post MJ, Berger JR, *et al*. Progressive multifocal leukoencephalopathy in 47 HIV-seropositive patients: neuroimaging with clinical and pathological correlation. *Radiology* 1993;**187**:233–40.
- 15 **Smirniotopoulos JG**, Koeller KK, Nelson AM, *et al*. Neuroimaging-autopsy correlations in AIDS. *Neuroimaging Clin North Am* 1997;**7**:615–37.
- 16 **Iranzo A**, Kulisevsky J, Cadafalch J, *et al*. Trastornos del movimiento asociados al sida. *Neurología* 1996;**11**:70–5.
- 17 **Nath A**, Jankovic J, Pettigrew LC. Movement disorders and AIDS. *Neurology* 1987;**37**:37–41.
- 18 **Tagliati M**, Simpson D, Morgello S, *et al*. Cerebellar degeneration associated with human immunodeficiency virus infection. *Neurology* 1998;**50**:244–51.
- 19 **Marseille Consensus Group**. Classification of progressive myoclonus epilepsies and related disorders. *Ann Neurol* 1990;**28**:113–16.
- 20 **Marsden CD**, Harding AE, Obeso JA, *et al*. Progressive myoclonic ataxia (the Ramsay Hunt syndrome). *Arch Neurol* 1990;**47**:1121–5.
- 21 **Bhatia KP**, Brown P, Gregory R, *et al*. Progressive myoclonic ataxia associated with coeliac disease. The myoclonus is of cortical origin, but the pathology is in the cerebellum. *Brain* 1995;**118**:1087–93.
- 22 **Agostini HT**, Ryschkewitsch CF, Mory R, *et al*. JC virus (JCV) genotypes in brain tissue from patients with progressive multifocal leukoencephalopathy (PML) and in urine from controls without PML: increased frequency of JCV type 2 in PML. *J Infect Dis* 1997;**176**:1–8.
- 23 **Woo HH**, Rezai AR, Knopp EA, *et al*. Contrast-enhancing progressive multifocal leukoencephalopathy: radiological and pathological correlations: case report. *Neurosurgery* 1996;**39**:1031–5.

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