Arq Neuropsiquiatr 2005;63(1):150-153

HEAD TREMOR AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY IN AIDS PATIENTS

Report of two cases

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ABSTRACT - Progressive multifocal leukoencephalopathy (PML) is caused by replication of JC virus in oligodendrocytes of immunocompromised patients. Common manifestations are focal motor and sensory deficits, gait abnormalities, speech and language disturbances, cognitive disorders, headache, and visual impairment. Although the occurrence of movement disorders is rare in PML, bradykinesia, rigidity, dystonia, myoclonic jerks and myoclonic ataxia have been described. Head tremor associated with PML has not been previously reported. We report two cases of PML in whom head tremor was present.

KEY WORDS: progressive multifocal leukoencephalopathy, tremor, movement disorders, AIDS.

Tremor cefálico e leucoencefalopatia multifocal progressiva em pacientes com SIDA: relato de dois casos

RESUMO - A leucoencefalopatia multifocal progressiva (LMP) é causada pela replicação do vírus JC em oligodendrócitos de pacientes imunocomprometidos. As manifestações mais comuns incluem déficits motores e sensitivos, alterações da marcha, da fala e da linguagem, cefaléia e distúrbios visuais e cognitivos. Embora a presença de distúrbios do movimento não seja tão freqüente na LMP, bradicinesia, rigidez, abalos mioclônicos e ataxia mioclônica já foram descritos. Nós relatamos dois casos de LMP associados com tremor cefálico.

PALAVRAS-CHAVE: leucoencefalopatia multifocal progressiva, tremor, distúrbios do movimento, SIDA.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system (CNS) caused by the JC virus strain of the papovavirus family. The virus infects and destroys oligodendrocytes, causing patchy areas of demyelination in the cerebral white matter. This disease occurs almost exclusively in immunocompromised individuals, particularly in patients with acquired immunodeficiency syndrome (AIDS), lymphoma and chronic and myeloproliferative diseases, and transplant recipients. Low CD4 cell count (<100 cells per microliter) is postulated to permit reactivation of latent JC virus resulting in the clinical expression of PML[1,2]. PML is present in up to 5% of AIDS patients, causing considerable morbidity and rapid progression to death within a few months[3,4]. Recently, highly active antiretroviral therapy (HAART) and other forms of antiviral treatment have been shown to increase survival in these patients[4,5] .

The clinical picture of PML is a consequence of progressive white matter destruction and varies with lesion location. The presenting manifestations of PML in patients with AIDS do not appear to differ substantially from those in patients with other immunosuppressive conditions. Common manifestations consist of focal motor and sensory deficits, gait abnormalities, speech and language disturbances, cognitive disorders, headache, and visual impairment[6]. Although the basal ganglia circuitry may be involved in the pathology of PML, movement disorders, at least at the onset of PML, are very rare. Bradykinesia and rigidity, dystonia, myoclonic jerks and myoclonic ataxia have been described[6-8]. Head tremor has not been described so far in such patients.

We now report two cases of PML in whom head tremor was present.

CASES

Case1 – A 33-year-old woman with AIDS for 3 years was admitted to our institution due to gait ataxia and

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Received 2 April 2004, received in final form 29 July 2004. Accepted 22 September 2004.

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Table 1. Cerebrospinal fluid findings.

	Case 1	Case 2
Leukocyte count (cells/μL)	6	1
Erythrocyte (cells/μL)	0	4
Cell type	lymphocytes	NA
Glucose (mg/dL)	78	84
Protein (mg/dL)	118	29
Bacterial culture	negative	negative
Gram stain	negative	negative
Mycobacteria culture	negative	negative
Fungal culture	negative	NA
Cryptococcus neoformans		
Antigen	negative	NA
Cytomegalovirus IgG	R	NR
Toxoplasma IgG	NA	NR
Toxoplasma IgM	NA	NR
Herpes simplex IgG	NR	NR
FTA-ABS	NR	NR
VDRL	NR	NR
Epstein-Baar virus PCR	negative	negative
JCV PCR	positive	positive
Toxoplasma gondii PCR	NA	negative
Herpes virus type 6 PCR	negative	negative
Herpes simplex type 1 and		
2 PCR	negative	NA
Herpes zoster PCR	negative	NA
Cytomegalovirus PCR	negative	negative
Mycobacteria PCR	negative	negative
Enterovirus PCR	negative	NA

R, reactive; NR, not reactive; NA, not available.

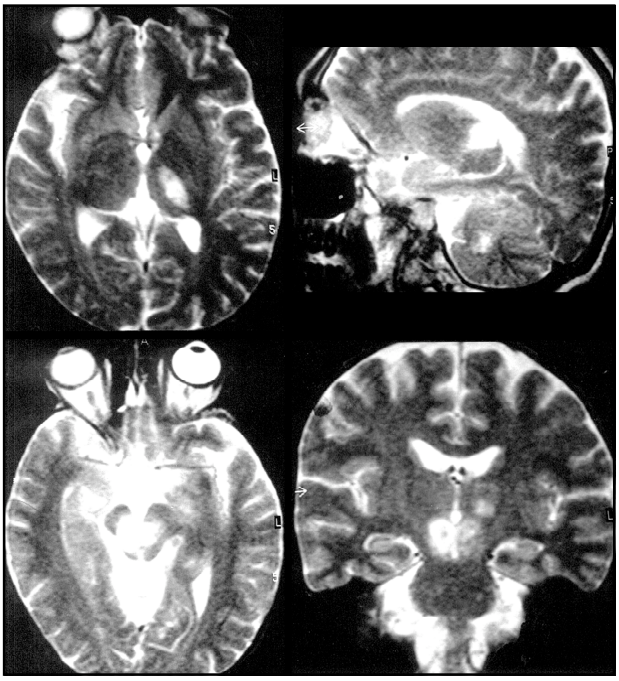

Fig 1. Cranial MRI (T2-weighted) showing hyperintensities in the left thalamus (a, b), cerebellum (b) and midbrain (c, d).

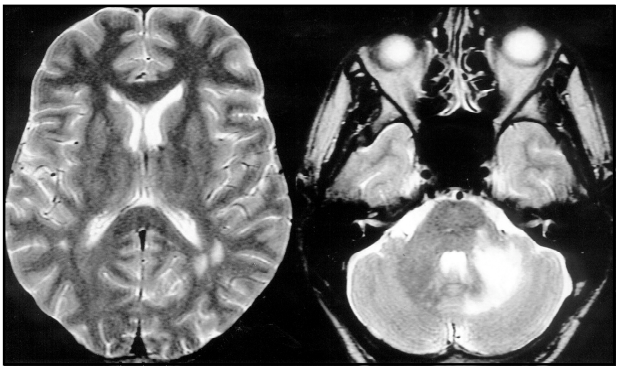

Fig 2. Cranial MRI (T2 weighted) showing hyperintense lesions in the white matter near the left occipital horn (a), cerebellum and left middle cerebelar peduncle (b).

speech disturbance along with blurred vision, which had insidiously developed in the previous four months. She had pulmonary tuberculosis one year before, and was treated successfully with isoniazid, rifampin and pyrazinamide for 9 months. She has been on multiple antiretroviral regimens, the last combination consisting of zidovudine, didanosine and indinavir. At admission her CD4 cell count was 253 cells/mm^3. On the neurological examination the patient was alert and fully. Her speech was dysarthric and she was unable to walk because of a severe gait ataxia. Sitting was difficult without support. The patient was quite ataxic on bilateral finger-to-nose and heel-to-knee testing. She had also a high amplitude 4 Hz "no-no" type of head tremor. The tremor persisted when lying down. It was intensified by voluntary movements and disappeared during sleep. She had a right-sided weakness and a dystonic posturing of the fingers of her right arm, and episodes of irregular distal arm tremor. Muscle tone was increased in both legs, and she had a right-sided hyperreflexia. Her plantar responses were flexor. Abduction of the right eye was impaired. Upward and downward gaze was impaired. An abducting nystagmus of the left eye was present. Pupils were 2 mm, round, isocoric, and reacted to light. Partial ptosis was observed in the left eyelid. EEG showed a diffuse increase in slow activity, with no evidence of cortical spikes. Lumbar puncture yielded a clear cerebrospinal fluid (CSF) under normal pressure and a positive JC virus PCR (Table 1). Viral serology was IgG positive for CMV and HSV. Serology for toxoplasma was positive for immunoglobulin G (IgG) and negative for IgM. VDRL, HTLV-I and II serology were negative. Magnetic resonance imaging (MRI) showed hyperintense lesions involving the thalamus, mesencephalon, red nuclei, pontine tegmentum and cerebellum without gadolinium enhancement or mass effect (Fig 1). During the following months the patient developed a spastic tetraparesis, anarthria and dysphagia, along with deterioration in her general physical condition. She

became comatose and died from *Staphylococcus aureus* pneumonia. No autopsy was performed.

Case 2 – A 51-year-old man presented with a 3-months history of progressive generalized weakness, dysarthria, dysphagia and visual difficulties. There were no sensory or sphincter dysfunction. His past medical history was unremarkable. He denied any history of known HIV infection, promiscuous bisexual or homosexual relationship, and exposure to blood or blood products. His physical examination at the time of admission revealed a gait and limb ataxia, and scanning dysarthria. Upward gaze of both eyes was impaired. Superficial and deep sensations were preserved. HIV-1 serology was positive using enzyme-linked immunosorbent assay technique. One week after admission he developed an intense isolated "no-no" type head tremor at rest, with increasing amplitude during maintenance of a fixed posture and intentional voluntary movements. During the following month the patient developed a symmetrical spastic tetraparesis, together with deterioration in his general physical condition. MRI showed hyperintense zones in cerebellum and cerebellar peduncle (Fig 2). CSF findings are shown in Table 1 with a positive JC virus PCR. In the subsequent month he developed severe cachexia, became comatose, and finally died of pneumonia.

DISCUSSION

As far as we know, head tremor associated with PML has not been previouly reported. The occurrence of movement disorders is uncommon in PML. Even in cases of HIV-related PML with basal ganglia involvement, focal movement disorders have rarely been reported[9]. Bradykinesia and rigidity may be detected in a minority of patients with advanced disease[7]. Dystonia and jerky movements of the hand have been observed as a consequence of contralateral lesions in the basal ganglia[6]. Myoclonic ataxia in a PML patient was recently described[8]. We now report two AIDS patients with head tremor in whom the appearance of white matter MRI lesions as well as a positive PCR test for JC-virus in the CSF led to the diagnosis of PML. In one case PML was the initial manifestation of AIDS.

Although PML lesions frequently begin in the parieto-occipital lobes they may occur virtually anywhere. The symptoms and characteristic radiologic findings of PML are due to virus-induced lysis of oligodendrocytes, resulting in microscopic foci of myelin breakdown that coalesce to produce increasingly larger lesions. Imaging is important in the diagnosis of PML. MRI demonstrates asymmetric areas of T1 hypointensity and T2 hyperintensity in the white matter. One third to one half of patients may have involvement of the posterior fossa, and in 5% to 10% the disease is confined to these structures[10-14]. Approximately 90% of HIV-infected patients who have PML at their initial evaluation have CD4 lymphocyte counts of fewer than 200 cells/mm^3. Amplification of the JCV genome by PCR is highly sensitive and specific for PML and it has been suggested that this diagnostic test may eliminate the need for brain biopsy[2].

Whilst head tremor is observed in other neurological conditions such as stroke, multiple sclerosis and head trauma its origin often remains unclear[14,15]. We believe that the involvement of structures in the dentate-rubro-thalamo-cortical pathway as documented by MRI, was responsible for the head tremor. Cases of cerebrovascular events due to midbrain infarction or thalamic lesions leading to head tremor have been published[15]. According to experimental studies head tremor may be generated by synchronized bursts of thalamic cells of the ventromedial nucleus[16], which was not affected in this case. Nevertheless, induction of tremor by lesions of other thalamic nuclei cannot be excluded in our first case.

The head tremor presented here resembles Holmes tremor. Holmes tremor, or rubral tremor, or midbrain tremor, is characterized by its presence at rest, enhancement during maintenance of a fixed posture, and increasing amplitude with intentional voluntary movements. Frequency is slow, usually between 2-4 Hz[17]. The anatomy of this tremor is complex and incompletely understood, but there has been broad agreement that the tremor follows interruption of the dentate projections pathways, particularly in the region of the superior cerebellar peduncle and red nucleus[18]. Since MRI revealed a lesion in the red nucleus, we conclude that the head tremor is most likely a rubral tremor due to PML.

Stereotactic lesions performed in monkeys in the parvicellular red nucleus, brachium conjunctivum decussation and ventromedial mesencephalon (substantia nigra) demonstrated that damage to all three areas was necessary for sustained tremor[19] .These findings confirm clinicopathologic observations in humans. A combination of damage to the red nucleus and neighboring cerebello-thalamic, cerebello-olivary, and nigrostriatal fibers tracts are required for the development of Holmes tremor (an association of rest, postural and kinetic tremor)[19].

In summary, the increasing spectrum of clinical and imaging findings being increasingly reported

in the literature suggest that PML should be considered in the differential diagnosis of all HIV positive patients with uncommon clinical presentations and MRI findings compatible with demyelination.

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