MYOCLONUS AS AN UNUSUAL PRESENTATION OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY IN A HIV POSITIVE PATIENT

L. Chicea[1], E.C. Rosca[1, 2], O. Rosca[3,4], M. Ciolan[1], M. Simu[1,2]

[1]Clinical Emergency County Hospital Timisoara, Department of Neurology II
[2]University of Medicine and Pharmacy "Victor Babes" Timisoara, Department of Neurology II
[3]Clinical Hospital of Infectious Diseases and Pneumophtisiology "V. Babes" Timisoara, Department of Infectious Diseases I
[4]University of Medicine and Pharmacy "Victor Babes" Timisoara, Department of Infectious Diseases I

ABSTRACT

From mild muscular contractions to gross jerks affecting the whole body, myoclonus is an involuntary movement caused by an excessive discharge from a group of neurons located in one or multiple sites from cortical to peripheral level.

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the CNS caused by oligodendroglial destruction due to JC virus. Usually it manifests with focal neurological deficits such as motor weakness, sensory abnormalities, visual disturbances, cognitive impairments, movement disorders having a low incidence in these patients. We report a rare case of myoclonus as a neurological complication of PML in AIDS, analyzing the link between the stage of HIV infection, the MRI lesions and the type of myoclonus, being also aware of potential interactions between the antiepileptic drugs and the antiretroviral therapy.

Key words: myoclonus, progressive multifocal leukoencephalopathy, HIV

BACKGROUND

Myoclonus is defined as a sudden, brief, shock-like involuntary movement caused by muscular contraction or inhibition, originating either in the central or peripheral nervous system (1). Described in 1881 by Friedreich as "paramyoklonus multiplex", it literally means „a quick movement of muscle" (2).

Myoclonus is the result of an excessive discharge from a group of neurons, the main pathophysiological categories being: cortical, cor tical-subcortical, subcortical-nonsegmental, segmental and peripheral.

Myoclonic manifestations can range from mild muscular contractions with small amplitude movement to gross jerks affecting the whole body (3). According to the distribution, myoclonus can be focal or segmental (confined to one particular region of the body), multifocal (different parts of the body are affected, not always at the same time) and generalized (whole body is affected in a single jerk).

The most common type is the cortical myoclonus which typically is stimulus-sensitive, being triggered by sudden noise, visual stimuli or muscle stretch. It consists in focal or multifocal muscle contractions, usually more distal than proximal and more flexor than extensor, the muscles being often activated in antagonist pairs.

Cortical-subcortical myoclonus results from the interaction of cortical and subcortical centers such

Author for correspondence:
Elena Cecilia Rosca, Department of Neurology, Clinical Emergency County Hospital, 10 Iosif Bulbuca Blv., Timisoara
e-mail: roscacecilia@yahoo.com

as the thalamus (3). Frequently, it is multifocal, the muscular contractions being bilaterally synchronous or generalized. The thalamic myoclonus usually affects the hand in the form of asterixis.

Subcortical-nonsegmental myoclonus arises from brainstem areas. The reticular reflex myoclonus originates in the caudal brainstem and spreads rostrally and caudally. It affects more the proximal muscles and the flexors are more active than extensors (4) causing generalized flexor jerks of the proximal upper and lower limbs and trunk. Usually it is severe and may be stimulus-sensitive.

Segmental myoclonus originates from segmental brainstem (palatal) or cervical and thoracic spinal cord. The spinal segmental myoclonus involves a restricted body part, may be rhythmic, sometimes is stimulus-sensitive and often persists during sleep (5). The propriospinal myoclonus arises from the thoracic spinal cord, but because the discharge spreads rostrally and caudally it is considered to be subcortical-nonsegmental myoclonus. It produces generalized axial movements (6).

Peripheral myoclonus arises within the plexus or the peripheral nerve (7,8). Unlike the majority of myoclonic movements, it persists during sleep. The most common form is the hemifacial spasm.

Myoclonic jerks can have many causes. They can be physiological (hypnic jerks and hiccough), essential (idiopathic, as the primary symptom, with a nonprogressive course), epileptic (occurring in the setting of a seizure disorder, usually associated with epilepsy in children) and symptomatic, accompanying seizures (progressive myoclonic epilepsy) or other large number of disorders (8,9,10). Most causes of myoclonus are symptomatic (11). The list of associated diseases is extensive and includes myoclonic dementias (Creutzfeldt-Jakob disease, Alzheimer disease), basal ganglia disorders (corticobasal degeneration, Lewy body disease, Parkinson disease, multisystem atrophy, Huntington's disease, panthotenate kinase 2 deficiency), acquired metabolic syndromes (including hepatic failure, uremia, hyponatremia, hypoglycemia and nonketotic hyperglycemia), drug-induced and toxic syndromes (anticonvulsants such as lamotrigine and gabapentin, levodopa, selegiline, amantadine, tricyclic antidepressants, neuroleptics, lithium, propofol, carvedilol, bismuth, methyl bromide), malabsorbtion syndromes (celiac disease), static encephalopathies secondary to diffuse brain injuries (hypoxia, trauma), opsoclonus-myoclonus syndrome, inflammatory syndromes (with antibodies to voltage-gated potassium channels).

Also, myoclonus was reported in various infections of the nervous system. Opsoclonus-myoclonus was described in patients with West Nile virus encephalitis (12), Dengue fever (13), Lyme disease (14) and encephalitis with cytomegalovirus (15), Epstein Barr virus (16), varicella zoster (17) and herpes 6 virus (18), infections with Mycoplasma pneumoniae (19), Streptococcus (20) and Salmonella (21). Myoclonus was frequently reported in patients with subacute sclerosing panencephalitis (22) and neurologic complications of Shiga toxin-producing enterohemorrhagic E Coli O104:H4 (23); occasionally it was described in Nipah virus encephalitis (24) and Dengue virus infection (25). The myoclonus – dystonia syndrome was reported in a Herpes virus 6 infection (26).

Movement disorders represent an important neurologic complication of HIV infection, being reported in up to 50% of the AIDS patients (27). They are the result of opportunistic infections, HIV encephalopathy or side effect of drugs. The most common dyskinesias are chorea and tremor (27), but myoclonus is also documented in these patients. Cortical myoclonus (28) and opsoclonus-myoclonus (29) were reported in HIV encephalopathy. Furthermore, myoclonus was also rarely documented in progressive multifocal leukoencephalopathy (PML) (30,31).

The present work is aimed to report myoclonus as an unusual presentation of PML in a HIV-positive patient.

CASE PRESENTATION

We report the case of a 23 years-old female with stage B3 HIV infection, which presented right upper limb myoclonus; the symptoms started one month ago and gradually worsened. She was diagnosed with HIV-1 infection 3 years ago and was currently on HAART therapy (atazanavir 300 mg/day, ritonavir 100 mg/day, lamivudine/zidovudine 150/300 mg 2x1/day).

On physical examination she had a temperature of 36.8˚C, blood pressure of 110/70 mmHg and a regular pulse of 72 beats/min. The chest, cardiovascular and abdominal examinations were all normal.

The neurologic examination revealed a conscious patient, with no signs of neck stiffness; on motor examination, there was a right upper limb arrhythmic, stimulus-sensitive myoclonus present in rest, but more pronounced in action and when maintaining a posture that disappeared during sleep

and brisk tendon reflexes in this limb. The rest of the neurological examination was unremarkable.

The diagnostic workup showed a CD4 cell count of 95 cells/µl, a CD8 cell count of 1029 cells/µl, with CD4/CD8 = 0.09 and a viral load (VL) of 225479 copies/ml. The CSF viral load was of 265 copies/ml. The lumbar puncture tests were negative for herpes viruses, adenoviruses, parvoviruses and enteroviruses, but positive for JC virus; the chemical and microbiological examination of CSF was normal.

The brain MRI scan revealed multiple non-enhancing millimetric lesions with high signal in T2 and FLAIR sequences, situated in the right pons, right middle cerebellar peduncle, right mesencephalon, left lentiform nucleus and subcortical lesions in the left temporal, frontal and occipital lobes (Fig. 1).

Based on clinical and paraclinical findings a diagnosis of PML was made. Although the laboratory tests showed no resistance of the virus to her previous HAART medication, the regimen was optimized and potentially CNS-active drugs were included; she started a HAART with lopinavir/ritonavir 200/50 mg 2x2/day, lamivudine/zidovudine150/300 mg 2x1/day, enfuvirtide 90 mg 2x1/day. Also the patient received sodium valproate/valproic acid (500 mg twice a day), with partial remission of symptoms. However, taking into account the possible interactions between the antiepileptic drug and HAART, she was changed to levetiracetam (500 mg twice daily) with a good response to the new therapy.

DISCUSSION

The present case raises several points for discussion: which are the lesions causing the symptoms, is JC virus responsible for them or are they due to HIVE, and which is the more appropriate treatment for this patient.

The most common cause of movement disorders in AIDS patients is cerebral toxoplasmosis (32), but other opportunistic infections of CNS should also be taken into account. In toxoplasmosis, granulomas are preferentially located in the basal ganglia, diencephalon, and midbrain. The clinicopathologic correlation is obvious in chorea-hemiballismus, the most common hyperkinesia in AIDS, resulting from subthalamic lesions caused by Toxoplasma gondii (27).

The first consideration must be given to the stage of HIV infection, which influences the risk of possible neurologic complications. Our patient had a CD4 cell count < 200/mm^3, with high risk of HIVE, primary CNS lymphoma, cerebral toxoplasmosis,

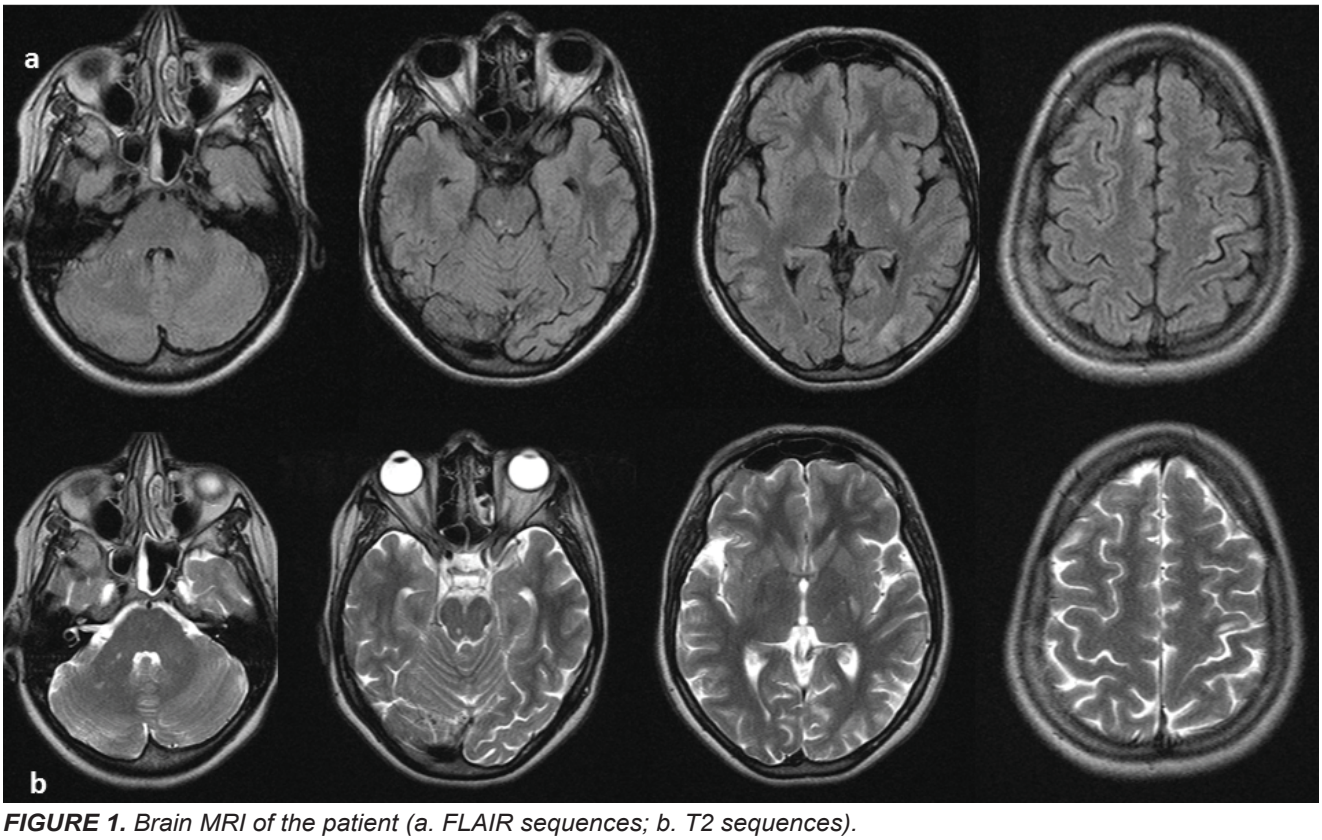

FIGURE 1. *Brain MRI of the patient (a. FLAIR sequences; b. T2 sequences).*

PML, CMV encephalitis and cerebral cryptococcosis. Although the clinical picture with myoclonus was suggestive for HIVE or cerebral toxoplasmosis, the MRI scan revealed multiple subcortical, bilateral, asymmetrical, non-enhancing lesions, with high signal in T2 sequences, a radiological picture more suggestive for PML than HIVE where the T2 hyperintense, non-enhancing lesions usually are periventricular, symmetrical (33). In PML, typically there are bilateral asymmetrical lesions, hyperintense in T2 sequences with no mass effect; usually the arcuate fibers are involved, with a parietal predominance. Other less common lesion sites are the basal ganglia, thalamus and the posterior fossa (33). Furthermore, the patient's CSF was positive for JC virus, clarifying the diagnosis.

The differential diagnosis between PML and HIVE is an important issue, as the 2 conditions have different prognosis. Although in the pre-HAART era the median survival was 183 days (34), prolonged survival has become more common since the introduction of HAART (35), usually being correlated with higher CD4+ cell counts, contrast enhancement and neurological recovery (35).

PML is a rare demyelinating disease of the CNS caused by oligodendroglial destruction due to JC virus. The infection with JC virus is an asymptomatic childhood infection that persists throughout life in a latent form affecting 80% of adults and can be reactivated in cases of immune deficiency such as AIDS. The large majority of PML cases are now observed in patients with AIDS with an incidence that approaches 5% (31). Viewed from another perspective, over three-quarters of the PML cases in the current era are associated with AIDS (23). Usually PML manifests with focal neurological deficits such as motor weakness, sensory abnormalities, visual disturbances, cognitive impairments; however, movement disorders have a low incidence (up to 2.6%) in these patients (36).

The present case reports a very unusual clinical presentation of PML, myoclonus being rarely documented in JC virus infection. Sweeney et al. reported the case of a HIV – positive patient with right hand athetoid and myoclonic movements and lower limbs action and stimulus-sensitive myoclonus; the pathological postmortem examination revealed a predominance of the grey matter and immediately subcortical structures with JC virus infection (30). Another case of progressive myoclonic ataxia in an AIDS patient with PML was published by Fontoura and his colleagues. Their patient developed ataxia and action and stimulus – sensitive myoclonus; the brain MRI revealed bilateral subcortical lesions and thalamic lesions which extended to the mesencephalon and red nuclei. In addition, the necropsy showed small and medium sized foci of demyelination extending from the subjacent gyral white matter into the deep cortical layers. The authors assumed that the myoclonus was of cortical origin (31).

In our patient, the multiple lesions found on MRI make it difficult to attribute the myoclonus to a specific lesion. However, the clinical picture of the myoclonus points to a cortical origin.

The mesencephalic lesion of our patient would more probably cause Holmes tremor, a predominantly proximal dyskinesia with large amplitude and low frequency, with rest, postural and kinetic components, worsened by action. The Holmes tremor was reported in HIV patients with Toxoplasma abscesses located in the mesencephalon or thalamus; it was assumed to be due to the interruption cerebello-thalamo-corical or the dentate-rubro-olivary pathways (37,38). Also, the middle cerebellar peduncle lesion seen on the brain MRI scan could have caused such a "wing beating" tremor (27). The basal ganglia lesion (lenticular nucleus) observed on the MRI scan could have been the anatomical substrate for asterixis (flapping tremor). However, clinically, our patient presented an arrhythmic dyskinesia, more suggestive for a cortical myoclonus.

Although the brain MRI revealed subcortical lesions, the presence of myoclonus points to a cortical origin of the symptoms. In the literature there are previous reports of grey matter lesions in PML, even without MRI abnormalities, some authors assuming that grey matter involvement is a secondary phenomenon related to white matter destruction (30,39). Other studies demonstrated that in up to 56% of the PML cases there is also involvement of deep gray matter including basal ganglia and thalamus, and even cortical gray matter of the gray-white junction (40,41). Recent findings also reported gray matter disease secondary to a productive infection of cortical pyramidal neurons, the authors arguing that PML lesions can extend into the grey matter since myelinated fibers present in the cortex (42,43,44). The genetic research progress has also lead to characterization of novel JC virus variants that causes productive infection of cortical neurons (45).

Because there is no known specific antiviral agent against JC virus, the current treatment goal is to restore the adaptive immune response with HAART.

For the symptomatic control of myoclonus, sodium valproate and valproic acid (250 to 4500 mg/day) has been reported to alleviate cortical myoclonus. Other effective drugs are levetiracetam (1000 to 3000 mg/day), clonazepam (4 to 10 mg/day), and piracetam (10 to 24 g/day). In our patient, after optimization of the HAART, she received levetiracetam instead of sodium valproate/valproic acid, with improvement of the symptoms. In HIV patients, there are potential interactions between the antiepileptic drugs and HAART therapy. Some earlier studies suggested that sodium valproate, due to its effects on the HDAC1 enzyme, can be useful reducing the amount of HIV stored within the DNA of CD4 T cells; this preliminary data was viewed as new approach to eliminate HIV infection in persistent reservoirs (46). However, further studies demonstrated that adding valproic acid to HAART does not change the size of the HIV reservoir (47,48). Some other animal and preliminary human studies in HIV infected patients suggested that it can improve brain impairment, ameliorating HIV-associated neurotoxicity (49,50) but other researchers did not confirm these data (51).

Furthermore, antiepileptics such sodium valproate, that inhibit the cytochrome P450 enzyme system, may increase the metabolism of certain antiretroviral drugs and conversely, patients receiving valproic acid may require a zidovudine dosage reduction (level C recommendation); for newer antiretroviral agents there is minimal data on their interactions with antiepileptic drugs (52). In accordance with these recommendations, after the patient's HAART regimen was established, she was changed on levetiracetam, a non-enzyme inducing drug. However, as there is not much data on the use of levetiracetam in HIV infected patients, she was careful monitored to ensure efficacy of the antiretroviral therapy.

The present case documents a rare case of PML with myoclonus as the sole neurological sign. The involvement of the grey matter is a probable cause for the symptoms. The present findings support the reappraisal of the JC virus CNS infections, the term of leukoencephalopathy being inadequate for the disease. Furthermore, the clinician should take into consideration the newly described clinical and radiological manifestations of PML when investigating a HIV – infected patient and also carefully manage the treatment with attention to possible drug interactions.

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