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HIV-Related Movement Disorders

Epidemiology, Pathogenesis and Management

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Contents

Abstract

Clinically relevant movement disorders are identified in 3% of patients with HIV infection seen at tertiary referral centres. In the same setting, prospective follow-up shows that 50% of patients with AIDS develop tremor, parkinsonism or other extrapyramidal features. Hemiballism-hemichorea and tremor are the most common hyperkinesias seen in patients who are HIV positive, but other movement disorders diagnosed in these patients include dystonia, chorea, myoclonus, tics, paroxysmal dyskinesias and parkinsonism. Patients with movement disorders usually present with other clinical features such as peripheral neuropathy, seizures, myelopathy and dementia.

In the vast majority of patients, hyperkinesias result from lesions caused by opportunistic infections, particularly toxoplasmosis, which damage the basal ganglia connections. On the other hand, parkinsonism and tremor can result from dopaminergic dysfunction resulting from HIV itself or the use of antidopaminergic drugs.

The management of patients who are HIV positive who present with movement disorders involves recognition and treatment of opportunistic infections, symptomatic treatment of the movement disorder and the use of highly active antiretroviral therapy (HAART). The most effective treatment of cerebral toxoplasmosis in patients with HIV infection is the combination of sulfadiazine and pyrimethamine. Symptomatic treatment of the movement disorder is often dis-

appointing: hemiballism improves with antipsychotics, but tremor, parkinsonism and other phenomena usually fail to respond to available therapies. Preliminary data suggest that HAART may be helpful in the symptomatic control as well as prevention of movement disorders in patients who are HIV positive.

The aim of this article is to describe the epidemiology, clinical manifestations, pathogenesis and treatment of movement disorders that occur in association with HIV infection.

1. Epidemiology

Neurological complications, observed in at least 60% of patients with AIDS, may result from opportunistic infections, a direct lesion caused by HIV and drug-induced adverse effects.[1]

Despite the lack of population-based, controlled epidemiological studies, movement disorders seem to account for a small proportion of neurological problems observed in patients with HIV infection. One retrospective chart review performed in a tertiary referral centre at the peak of the AIDS epidemic, for instance, found movement disorders in just 3% of patients who were HIV positive.[2] This and many other studies indicate that hemichorea-hemiballism is the most common movement disorder reported in association with HIV infection.[3] A more recent study[4] indicates that progression of HIV infection increases the frequency of movement disorders. After prospectively examining patients attending a NeuroAIDS clinic, the investigators showed that tremor and parkinsonian signs were detected in almost 50% of the patients, of whom 5% met criteria for parkinsonism. Another study[5] estimated that 5.5% of patients with HIV encephalopathy display tremor, although with progression of the disease this figure rises to 44%.[6] Thus, unlike previous studies, this one suggests that tremor is the most common movement disorder associated with HIV infection. With the introduction of highly active antiretroviral therapy (HAART), there is evidence of a decline in the incidence of neurological complications, including movement disorders, in patients with AIDS.[7]

2. Clinical Features

2.1 Hyperkinetic Movement Disorders

Hemichorea-hemiballism is usually an acute complication in patients already diagnosed with AIDS. However, in a few instances this movement disorder may be the presenting symptom of HIV infection.[8] In most patients the chorea is focal or involves one-half of the body only (hemichorea).

Patients with HIV infection may also develop generalised or focal dystonia.[9] Paroxysmal dyskinesias were described in six patients in a report a few years ago. Unfortunately, the clinical description provided by the authors does not allow one to classify the movement disorders of these patients as kinesiogenic, nonkinesiogenic or exercise-induced paroxysmal dyskinesias.[10] Other hyperkinetic movement disorders described in patients with HIV infection include action cortical, spinal or peripheral segmental myoclonus; akathisia; neuroleptic malignant syndrome; painful legs and moving toes syndrome; tics; and oculomasticatory myorhythmia associated with Whipple's disease.[2,10-13]

2.2 Parkinsonism and Tremor

Patients with AIDS may develop parkinsonism, in the absence of opportunistic infections, as part of HIV encephalopathy.[2,4] These patients often display a non–levodopa-responsive syndrome characterised by rigidity, bradykinesia and postural instability without the typical pill-rolling rest tremor. In one report,[14] however, the authors claim that levodopa improved parkinsonism associated with AIDS in children. In a study[4] performed in a NeuroAIDS clinic, showing parkinsonism in about 5% of the patients, the majority of patients presented with additional clinical signs such as dementia, seizures, vacuolar myelopathy and peripheral neuropathy.

Isolated tremor sharing the same pathogenesis

with parkinsonism is often seen in patients who are HIV positive. Typically, the movement disorder is an isolated, mild bilateral postural tremor, but rarely patients display an additional kinetic component.[15] Many of the patients with tremor, with or without other parkinsonian signs, have been exposed to antidopaminergic drugs.[4,15]

The tremor usually seen in patients with HIV infection has a postural component, visible when the patient keeps the arms outstretched, often in combination with a kinetic component. Less frequently there is a resting component. In addition to tremor associated with HIV encephalopathy, the Holmes tremor (formerly called rubral or midbrain tremor) with rest, postural and kinetic components can be seen in patients with AIDS. These patients often present with associated signs of midbrain dysfunction such as paresis of the oculomotor nerve and contralateral hemiparesis. Other tremors seen in patients who are HIV positive, including drug-induced tremor, usually occur in the context of HIV encephalopathy. One possible exception is cotrimoxazole (trimethoprim-sulfamethoxazole), which has been described as producing rest or action tremor without parkinsonism in patients with or without encephalopathy.[16,17]

HIV-associated tremor is seldom severe enough to require treatment. However, its recognition is important in defining the prognosis, since its presence usually suggests severe disease. For instance, one study[18] showed that 76% of patients with this and other movement disorders who were at Center for Disease Control stage IVA-D died during a 2-year follow-up, although this study was performed in the pre-HAART era.

3. Pathogenesis

Hyperkinesias in patients with AIDS are almost invariably caused by a *Toxoplasma gondii* abscess. Alternative causes include *Treponema pallidum* or *Cryptococcus neoformans* infection, progressive multifocal encephalopathy, primary lymphoma of the CNS, vacuolar myelopathy, HIV encephalopathy and drugs.[2,4,8,11,12,16,17,19] The lesions caused by opportunistic infections produce hyperkinesias by damaging the basal ganglia or its connections. For instance, granulomas in the subthalamus may cause hemichorea-hemiballism and in the cerebellar outflow pathways may lead to Holmes tremor.[3,15] The mechanism underlying tremor associated with exposure to cotrimoxazole in patients with AIDS remains to be determined, but there is a speculation that this drug causes disruption of dopamine production as a result of glutathione or tetrahydrobiopterin deficiency.[17]

There is a growing body of evidence indicating that HIV encephalopathy is associated with severe damage to the dopaminergic basal ganglia system. Some of the findings supporting this conclusion are reduced levels of dopamine and homovanilic acid in the CSF and neuronal loss in the pallidum of patients with HIV infection.[10,20] These results not only explain the occurrence of movement disorders in patients with AIDS who have HIV encephalopathy and their susceptibility to the development of movement disorders when exposed to dopamine receptor–blocking drugs, they also account for the pattern of cognitive decline seen in these patients, which is similar to that seen in subcortical dementias.[21] In fact, the most common cause of parkinsonism and tremor in patients with AIDS is HIV encephalopathy associated with damage to the basal ganglia, resulting in decreased dopaminergic activity.[2,4,15,20]

A recent study[22] using positron emission tomography has confirmed the crucial role played by basal ganglia dysfunction in the pathogenesis of motor and cognitive disturbances in HIV encephalopathy. According to these authors, the first abnormality identified in patients who are HIV positive, hypermetabolism of the basal ganglia, is not associated with any motor sign. However, when the patients develop mild hypometabolism of this area, there is moderate bradykinesia. Later, when diffuse basal ganglia hypometabolism is found, the patients present with severe motor slowing and dementia. As antidopaminergic drugs are associated with at least 50% of reported cases of parkinsonism in patients who are HIV positive, it may be concluded that even patients without overt parkin-

sonian symptoms and signs often have a preclinical dopamine dysfunction.[2,4] The mechanism responsible for dopamine cell loss in HIV encephalopathy remains to be determined, although excitotoxicity has been suggested to play a role.[23]

Toxoplasmosis abscesses, parenchymatous tuberculosis granuloma and neoplasms such as lymphoma have also been reported as reversible causes of parkinsonism in patients with AIDS.[24,25]

4. Management

4.1 Diagnosis

In most cases, when a patient presents with a movement disorder they are already known to be HIV positive. However, occasionally hemichorea-hemiballism may be the first manifestation of AIDS. For this reason, all patients with this hyperkinesia should undergo investigation for HIV infection.

The investigation of patients suspected of having movement disorders associated with HIV infection is targeted at identifying opportunistic infections. A computed tomography scan or magnetic resonance imaging of the head usually shows the typical findings of toxoplasmosis: multiple contrast-enhancing lesions with mass effect and surrounding oedema in the contralateral basal ganglia. The definite diagnosis of cerebral toxoplasmosis, however, depends on cerebral biopsy findings. This procedure is reserved for patients with negative serology for *T. gondii* or progressive clinical or radiological deterioration despite empiric antitoxoplamosis therapy for 2 weeks.[1] Even the use of prophylaxis against toxoplasmosis has not changed this policy substantially. Antinori et al.,[26] for instance, demonstrated that the chance of cerebral toxoplasmosis is still 59% in a *T. gondii*–seropositive patient undergoing prophylaxis, based on a prospective follow-up of 136 patients with AIDS who had focal brain lesions. They recommend performing a polymerase chain reaction assay for Epstein-Barr virus DNA and *T. gondii* in the spinal fluid. If the former is negative and the latter positive, there is a 0.99 probability of toxoplasmosis, and empiric therapy should be started.

In practice, CSF studies are not done in patients with intracranial hypertension because of the high risk of brain herniation. Under these circumstances, it is safer to start antitoxoplamosis treatment and to perform lumbar puncture in cases where the drug treatment fails and there is no radiological evidence of intracranial hypertension. Investigation of alternative causes is pursued in cases where the workup indicates that toxoplasmosis is not responsible for the movement disorder.

Images similar to those seen in patients with toxoplasmosis can be found in those with primary lymphoma as well as other opportunistic infections such as cryptococcosis, although the latter usually presents with diffuse meningoencephalitis. HIV encephalopathy often causes hypersignal of the basal ganglia on T2 images of this brain region.

4.2 Treatment of HIV and Opportunistic Infections

The most effective treatment of cerebral toxoplasmosis in patients with HIV infection is the combination of sulfadiazine and pyrimethamine.[1] Clindamycin with pyrimethamine, although equally effective for short-term treatment, is associated with a higher occurrence of long-term relapses.[1]

There are no published studies of HAART in the treatment of hyperkinesias associated with HIV infection. However, based on preliminary data indicating that neurological complications in general and motor slowing in particular become less frequent after starting this treatment, it may be speculated that HAART reduces the incidence of hyperkinesias associated with HIV infection.[7,27] Nevertheless, it should be emphasised that there is still controversy regarding this issue because HAART may not improve psychomotor slowing in all patients.[1,7]

4.3 Symptomatic Treatment

Symptomatic treatment of HIV-associated movement disorders depends on the clinical phenomenon present in a given patient.

4.3.1 Hemichorea-Hemiballism

Improvement of hemichorea-hemiballism is often seen after treatment of toxoplasmosis. In some cases, however, the patient remains disabled by the movement disorder despite such treatment. Drugs usually employed in the management of chorea, such as dopamine receptor–blocking drugs, reserpine, tetrabenazine and valproic acid (sodium valproate), may be helpful. However, the use of these medications is often complicated by the increased susceptibility of patients with AIDS to adverse effects such as dystonia, parkinsonism and tremor.[1,2,4,8,16,17] It is not rare, for instance, to have a patient with hemichorea-hemiballism that is controlled by antipsychotics to develop parkinsonism on the other side of the body.

4.3.2 Tremor

Empirical therapy for toxoplasmosis commonly fails to improve tremor associated with HIV infection. Levodopa, anticholinergics, clonazepam, propranolol, primidone, carbamazepine and isoniazid may help some patients who remain with disabling tremor.[15] Unfortunately, no drug is consistently effective for midbrain tremor.[28]

Of course, the best treatment for drug-induced movement disorders is the discontinuation of the offending agent.

4.3.3 Parkinsonism

Management of HIV-associated parkinsonism is based on the treatment of opportunistic infections, use of antitremor drugs and use of HAART. Although reports of the effect of levodopa in these patients are not encouraging,[1,3,14] a 4-week trial of levodopa/carbidopa 125/12.5mg three times a day is worth pursuing. Occasionally, one finds a patient with a good therapeutic response.

As discussed in section 4.2, the role of HAART in the treatment of parkinsonism and other movement disorders remains to be determined. Preliminary data suggest, however, that the combination of antiretroviral drugs with action in the CNS (zidovudine, stavudine, lamivudine, abacavir, nevirapine, efavirenz and indinavir) may prevent the occurrence of movement disorders and help their symptomatic management.[1,7,27] Recently, Hersh et al.[29] reported on one patient whose presenting manifestation of HIV infection was parkinsonism, which improved with HAART.

One important practical issue is the observation of complex pharmacokinetic interactions between antiretroviral drugs and many agents commonly used in neurology. Because of these interactions, dosage of the latter may have to be decreased. Obviously, for this reason, before prescribing any drug to patients receiving HAART, careful assessment of the pharmacological profile of the agent is required.

5. Conclusion

Clinically meaningful movement disorders are not common in patients with HIV infection; however, extrapyramidal features can be found in up to 50% of patients carefully examined. Tremor and hemiballism-hemichorea as a result of toxoplasmosis of the basal ganglia are the most common hyperkinesias seen in association with HIV infection. Parkinsonism, resulting from nigro-striatal dysfunction related to HIV encephalopathy and often triggered by exposure to antidopaminergic drugs, is observed in about 5% of patients who are HIV positive. Management of movement disorders associated with HIV infection is centred on identification and treatment of opportunistic infections, symptomatic treatment targeted at the phenomena observed and HAART.

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