Movement disorders and AIDS: a review

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Abstract

Movement disorders are a potential neurologic complication of acquired immune deficiency syndrome (AIDS), and may sometimes represent the initial manifestation of HIV infection. Dopaminergic dysfunction and the predilection of HIV infection to affect subcortical structures are thought to underlie the development of movement disorders such as parkinsonism in AIDS patients. In this review, we will discuss the clinical presentations, etiology and treatment of the various AIDS-related hypokinetic and hyperkinetic movement disorders, such as parkinsonism, chorea, myoclonus and dystonia. This review will also summarize current concepts regarding the pathophysiology of parkinsonism in HIV infection.

Keywords: Parkinsonism; AIDS; Human immunodeficiency virus; Movement disorders; Dopamine; Chorea

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1. Introduction

Neurologic disorders are a well-known complication of human immunodeficiency virus (HIV) infection [1]. Movement disorders are increasingly recognized as a potential complication of acquired immune deficiency syndrome (AIDS) and may sometimes represent the initial manifestation of HIV infection [2]. A 2–3% incidence of movement disorders has been reported in various HIV-infected populations studied retrospectively at tertiary referral centers [3]. However, when carefully evaluated in prospective studies, the incidence of movement disorders, and particularly parkinsonism, in AIDS patients appears to be higher than previously appreciated. Prospective studies have shown evidence of basal ganglia dysfunction, particularly tremor and parkinsonism, in 5–44% of patients [4].

In this review, we will discuss the different hyperkinetic and hypokinetic movement disorders seen in the setting of HIV infection, including hemichorea–hemiballism [5], myoclonus [6], dystonia [7], parkinsonism [8], tremor [9], and paroxysmal dyskinesias [10]. We will also review movement disorders seen in association with HIV-associated dementia (HAD), AIDS-related opportunistic infections or due to medications.

Motor dysfunction in the form of generalized slowness of movements seen in the setting of global cognitive and behavioral abnormalities has been termed the AIDS dementia complex (ADC) [11]. In this syndrome, cognitive symptoms mimicking a subcortical dementia usually precede motor symptoms, which most often include a slowing of rapid movements of the eyes and limbs. Other terms have been used to refer to this constellation of motor and cognitive abnormalities, including HAD, HIV encephalopathy and in milder forms, HIV associated minor cognitive/motor disorder [11]. For the purposes of this review, we will heretofore refer to this complex of dementia and motor dysfunction in HIV patients as HAD. It should be noted that HAD is distinct from HIV encephalitis, which is a neuropathologic diagnosis rendered when there is histologic evidence of HIV-induced inflammatory lesions in the brain. Approximately 50% of those individuals dying from HAD will have HIV encephalitis [12].

2. Tremor

2.1. Epidemiology of tremor

The reported incidence of tremor in AIDS patients has ranged from 5.5 to 44% of patients with HAD [9]. As HAD is a late-stage manifestation of HIV infection, this may suggest an increased incidence of tremor with increasing immunosuppression [13].

2.2. Clinical features and etiology of tremor

Tremor in AIDS patients may be seen as part of a parkinsonian (Table 1) syndrome or may occur as an isolated phenomena. The tremor is often symmetrical and may occur at rest, but more typically occurs as a mild bilateral postural tremor. Rarely patients may also display an additional kinetic component [14].

Tremor is often seen as one of the neurologic manifestations of HAD in both early and late stages of the illness. In the early stages of HIV infection, tremor may occur in the absence of clinically detectable central nervous system (CNS) deficit, and may precede the appearance of dementia by weeks to months [15].

Holmes tremor (also known as rubral or midbrain tremor) has been reported in AIDS patients, comprising a tremor with rest, postural and kinetic components [14]. Holmes tremor may occur as a result of opportunistic lesions in the midbrain such as tuberculosis or toxoplasmosis, and may also present with other focal neurologic signs suggesting a midbrain localization, such as ophthalmoplegia and contralateral hemiparesis [3,16].

Drug-induced tremor may be observed as part of an extrapyramidal syndrome seen in AIDS patients exposed to dopamine receptor antagonists such as neuroleptics or anti-emetics. An unusual complication of trimethoprim-sulfamethoxazole (TMP/SMX) therapy in AIDS patients for pneumocystis carinii pneumonia (PCP) is tremor, manifesting either as a rest tremor, or as a bilateral, high-frequency, low amplitude postural tremor with a kinetic component [17]. The postulated mechanism of tremor production with TMP/SMX treatment is reduction of catecholamine neurotransmission through inhibition of the enzyme dihydrofolate reductase (DHFR), which catalyzes the production of tetrahydrobiopterin [18]. It has been
<table>
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<tr>
<td>Tremor</td>
<td>Yes</td>
<td>(1) HIV infection (2) HAD (3) Tuberculosis—one patient with Holmes’ tremor (also called rubral or midbrain tremor) was described in association with tuberculosis lesions in the midbrain and cerebellum (4) Drug-induced—a rest, postural or kinetic tremor may be seen in patients taking trimethoprim/sulfamethoxazole (TMP/SMX) or as part of an extrapyramidal syndrome seen in AIDS patients exposed to dopamine receptor antagonists</td>
<td>Tremor in AIDS patients may be seen as part of a parkinsonian syndrome or may occur as an isolated phenomena. Tremor is often symmetrical and typically occurs as a mild bilateral postural tremor. Rarely patients may display an additional kinetic component. Tremor in patients with HAD may be seen in all stages of the illness</td>
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<td>Chorea–Ballism</td>
<td>Yes</td>
<td>(1) Subthalamic toxoplasmosis abscess (2) HIV encephalitis (3) HAD—has been described in association with generalized chorea (4) Cryptococcus (5) Progressive multifocal leukoencephalopathy (PML)—has been reported in association with focal chorea in one patient (6) Drug-induced—one case of focal chorea described after treatment with dopamine and noradrenaline for hypovolemic shock</td>
<td>Subthalamic toxoplasmosis abscess is the most common cause of hemichorea-hemiballism in AIDS patients. Some authors suggest that hemichorea-hemiballism in AIDS patients is virtually pathognomonic of cerebral toxoplasmosis</td>
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<td>Dystonia</td>
<td>No</td>
<td>(1) Basal ganglia toxoplasmosis—hemidystonia has been reported in association with contralateral toxoplasmosis lesions (2) HAD (3) Drug-induced—due to dopamine receptor antagonists (4) Bilateral putaminal lesions of unclear etiology—has been described in one patient with generalized dystonia, and left frontal lobe lesion of unclear etiology—has been described in one patient with acute paroxysmal dystonia</td>
<td>Patients with HAD appear to have an increased susceptibility to developing dystonia when treated with dopamine receptor antagonists</td>
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<td>Myoclonus</td>
<td>No</td>
<td>(1) HIV infection (2) HAD—has been described in association with generalized myoclonus (3) Toxoplasmosis—has been described in association with generalized myoclonus (4) Mycobacterium tuberculosis—has been described in association with spinal myoclonus (5) Herpes zoster radiculitis—has been described in association with segmental myoclonus (6) Progressive multifocal leukoencephalopathy—has been reported in one patient with diffuse cortical and subcortical lesions presenting with progressive myoclonic ataxia</td>
<td>Spinal myoclonus has been described as an unusual and early manifestation of HIV infection</td>
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<td>Paroxysmal dyskinesias</td>
<td>No</td>
<td>(1) Lesion in left frontal region of unknown etiology—has been reported in association with paroxysmal non-kinesigenic dystonia (2) HAD</td>
<td>Patients with both paroxysmal kinesigenic and nonkinesigenic dyskinesias have been reported. Patients with paroxysmal kinesigenic dyskinesias improved with benzodiazepines while only one patient with paroxysmal nonkinesigenic dyskinesias improved with benzodiazepines</td>
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suggested that TMP/SMX-induced tremor may be responsive to a reduction in dosage [19,20].

Finally, in a study done prior to the use of highly active antiretroviral therapy (HAART), abnormal motor function in AIDS patients, including the presence of tremor, was an indicator of underlying prognosis. Patients with HAD and early detectable motor impairment died within a 2-year period of cerebral AIDS manifestations, including HIV encephalitis and other opportunistic infections. In contrast, patients with normal motor performance only showed a slight deterioration over a 2-year period accompanied by decreasing T-helper cell counts. It was hypothesized that sensitive motor tests could serve as predictors for cerebral disease progression [15].

2.3. Treatment of tremor

Treatment of isolated tremor accompanying HIV infection has not been well studied. Evaluation of tremor should involve recognition of possible opportunistic infections and treatment of any underlying conditions. Drugs which may cause tremor should also be evaluated. De Mattos et al. described one patient with Holmes’ tremor associated with tuberculomas in the midbrain and cerebellum in which the mass lesions and tremor resolved with treatment of the tuberculosis [21].

3. Parkinsonism

3.1. Epidemiology of parkinsonism

Mirsattari et al. found a 5% incidence of parkinsonism in 115 HIV-infected patients who fulfilled United Kingdom Parkinson’s Disease Brain Bank (UKPDBB) criteria for the diagnosis of parkinsonism, as well as an additional 10 patients with parkinsonian features who did not meet the UKPDBB criteria [4]. One prospective study found that 50% of HIV inpatients with movement disorders had features of parkinsonism. The same study found a similar mean time of five months between HIV diagnosis and the onset of parkinsonism, and between parkinsonism and death, suggesting that parkinsonism represents a poor prognostic sign in AIDS patients [15]. Mirsattari et al. found that all HIV positive patients who presented with parkinsonism had severe immunosuppression as evidenced by a mean CD4 cell count of 14 cells/mm³ (range 0–40) at the time of diagnosis [4].

3.2. Clinical features of parkinsonism

The parkinsonism seen in AIDS patients is often atypical in presentation, with symmetrical signs of bradykinesia and rigidity, frequent lack of rest tremor, and early presentation of postural instability and gait difficulty [2].

Parkinsonian features may develop due to HIV infection, HAD, or due to underlying opportunistic infections such as cerebral toxoplasmosis (Table 2). A drug-induced extrapyramidal syndrome has also been reported. Further clinical features will be described under specific etiologies below.

3.3. Parkinsonism and HIV infection

Isolated parkinsonian features are common in HIV-infected patients. Mirsattari described five HIV-infected patients who developed parkinsonism in the absence of opportunistic infections, thus implicating HIV infection as the cause of parkinsonism [4]. Hersh et al. describe one HIV-infected patient who presented initially with atypical parkinsonism with lack of rest tremor, early bilateral signs on exam as well as early balance impairment. The parkinsonism improved initially with carbidopa/levodopa treatment and finally resolved on HAART [22].

3.4. Parkinsonism and HIV-associated dementia

HAD consists of a constellation of impairment in cognitive, motor and behavioral functions. AIDS patients who develop parkinsonism in the absence of opportunistic infections often suffer from HAD [23,24]. Navia et al. noted that motor symptoms are present early in nearly one-half of patients with HAD, and deterioration in handwriting, reflecting either a loss of motor coordination or tremor, was seen in six of 44 patients. Tremor may be seen throughout all stages of illness [13]. Parkinsonian features are common manifestations of HAD, including bradykinesia, rigidity, hypomimetic facies, postural instability and hypophonia [25,26,27]. In Navia et al.’s series of 70 patients with HAD, a rapid postural tremor was prominent in seven patients [13].

The cognitive disturbances characteristic of HAD are consistent with a subcortical dementia, which may also be seen in advanced Parkinson’s disease. This may include a slowing of thought, forgetfulness, apathy and poor sequential processing [28,29].

Even in the early stages of HIV infection in which there is no clinically evident CNS deficit, sensitive motor tests may detect subtle impairments of motor function, i.e. slowing of rapid alternating finger movements, and presence of postural tremor, which precede structural alterations seen on neuroimaging [26]. Motor performance deficits in early HIV disease as detected by electrophysiologic testing undergo rapid deterioration in the presence of HAD [30]. These deficits may precede dementia and radiological abnormalities up to several years [15].

With progression of HAD, there is also a progression of the motor and behavioral symptomatology. Early in the illness, forgetfulness, loss of concentration and behavioral changes are common, and motor symptoms include progressive loss of balance and deterioration in handwriting. In late stages, many patients develop global cognitive dysfunction accompanied by psychomotor retardation, and
may exhibit ataxia, hypertonus, weakness and spontaneous tremor or myoclonus [13].

3.5. Parkinsonism in AIDS patients with opportunistic infections

Parkinsonism in AIDS patients has been well described as a rare presentation of an underlying opportunistic infection. Patients with bilateral basal ganglia toxoplasmosis lesions have been reported as presenting with parkinsonian features. Sometimes these patients will manifest with other focal neurologic features which reflect the underlying lesions, or may exhibit other neurologic findings reflecting concomitant HIV-related involvement of other parts of the CNS [8,31]. Parkinsonism has also been reported in small case reports in association with progressive multifocal leukoencephalopathy [32], CNS tuberculosis [33], and Whipple’s disease [2].

3.6. Drug-induced parkinsonism and AIDS

Exposure to dopamine receptor antagonist medications, such as neuroleptics and anti-emetics is a common cause of drug-induced parkinsonism in AIDS patients. In fact, AIDS patients are particularly susceptible to developing extrapyramidal side effects from these medications. Hriso et al. reported that AIDS patients treated with neuroleptics were 2.4 times as likely to develop an extrapyramidal syndrome as psychotic patients without AIDS, and were 3.4 times as likely to develop an extrapyramidal syndrome when treated with haloperidol [34]. Severe drug-induced parkinsonism has been described in AIDS patients even when given low-potency neuroleptics such as prochlorperazine and low doses of anti-emetics such as metoclopramide [35,36]. Some authors hypothesize that this increased susceptibility is due to direct infection of the basal ganglia by HIV [37,38] or may be the result of an underlying preexistent subclinical nigral degeneration [4].

Potential drug interactions involving anti-HIV medications may also predispose patients to develop parkinsonism. Protease inhibitor medications have been reported to produce parkinsonian symptoms in one patient through an interaction of ritonavir and buspirone [39]. Indinavir has also been reported to potentiate the effect of levodopa in a patient with parkinsonism [40]. Antiprotease medications are known to inhibit the hepatic metabolism of several drugs by inhibition of cytochrome P450, which catalyzes oxidative reactions produced by monoamine oxidase (MAO) or catechol-O-methyltransferase (COMT). It was hypothesized that the enhanced effect of levodopa in this patient may be secondary to this effect.

3.7. Pathophysiology and neuropathology of parkinsonism

There is substantial evidence from neuroradiologic and pathological studies supporting dysfunction of the basal
ganglia in HIV infection. Neuroimaging studies have demonstrated selective basal ganglia atrophy in patients who develop HAD [41]. Progressive caudate atrophy has been significantly correlated with the presence of HAD [42].

Functional imaging studies have demonstrated dysfunction of basal ganglia metabolism in HIV-infected patients. Positron emission tomography (PET) studies have shown relative hypermetabolism in the basal ganglia and thalamus in the early stages of HIV dementia, with global cerebral hypometabolism noted in more advanced stages [43]. Cerebrospinal fluid (CSF) neurotransmitter studies have shown evidence of dopaminergic dysfunction in HIV infection. Dopaminergic neuron dysfunction appears to occur early in the course of HIV infection, with an apparent correlation between low CSF dopamine levels and declining immune function as reflected by CD4 lymphocyte counts. It was suggested that reduction of CSF dopamine levels may antecede CNS dysfunction, with a greater reduction of CSF dopamine levels seen in AIDS patients with symptomatic neurologic disease compared to asymptomatic patients [44]. Reduced caudate nucleus concentrations of dopamine and homovanillic acid (HVA) in AIDS patients compared to controls have been demonstrated [45].

Neuropathologic studies have shown preferential involvement of subcortical areas in HIV infection and involvement of the basal ganglia is well documented. Approximately 50% of patients with HAD demonstrate a microglial nodule encephalitis with multinucleated giant cells, with prominent involvement of the putamen and caudate nuclei [12]. Other opportunistic disorders in HIV may also demonstrate a predilection for the basal ganglia, such as toxoplasmosis, lymphoma and cryptococcus. The substantia nigra may also be affected in HIV. Reyes et al. showed nigral degeneration with neuronal loss, extracellular melanin and reactive astrocytosis in clinically asymptomatic AIDS patients [46]. Morphometric analysis of neurons in the substantia nigra pars compacta showed a significant reduction in numerical density of total neurons as well as of pigmented neurons, although the pattern of neuronal loss was different from that of both PD and normal aging in that the density of non-pigmented small neurons was reduced in HIV patients. It has been suggested that the nigral degeneration seen in AIDS patients may explain the increased susceptibility to drug-induced parkinsonism [47].

Several mechanisms have been proposed to explain the genesis of neurologic abnormalities in HIV infection. One hypothesis is that infection of mononcytid cells (macrophages, microglia or monocytes) by HIV stimulates the production of potential neurotoxins. These toxins include HIV proteins (i.e. gp120, tat) [27,48], and other substances produced by macrophages, including but not limited to glutamate, cytokines, nitric oxide, and quinolinic acid [45]. The HIV-1 envelope glycoprotein gp120 and the HIV-1 nuclear protein tat have been shown to be associated with neuronal injury in tissue culture experiments [49]. In animals infected with HIV, exposure of dopaminergic neurons to the gp120 protein reduced the ability of the neurons to transport dopamine [50] and this effect was blocked by NMDA receptor antagonists (MK-801) [51].

3.8. Treatment of parkinsonism

In patients with parkinsonism, management should focus on evaluation for potential underlying opportunistic infections and a careful review of the patient’s medications for potential extrapyramidal side effects. Treatment of any underlying infection is essential to controlling the movement disorder. There are no reported series of adult patients treated with levodopa to draw any firm conclusions regarding its efficacy in the treatment of parkinsonism in HIV, although one case report describes an adult patient having a good response [40]. Levodopa has been reported to be effective in improving motor function in a series of five HIV-infected pediatric patients with parkinsonian symptoms secondary to HAD [52]. However, there has been concern raised about the potential of dopamine to accelerate HIV infection and induce brain pathology in AIDS patients. Administration of selegiline and levodopa to monkeys with early simian immunodeficiency virus infection (SIV, a monkey model of HIV infection) accelerated the onset of neuropathologic changes, including CNS vacuolization and SIV encephalitic lesions [53]. Dopamine has also been found to activate HIV protein expression in HIV-treated T lymphoblasts [54].

HAART has been shown to be effective in the reduction of neurologic complications of HIV infection [55], and shows potential as a treatment for parkinsonism in the setting of HAD. HAART has been shown to improve the electrophysiological parameters of motor impairment in HIV infection, as demonstrated by significantly longer latencies to the development of pathologically prolonged contraction times [15,28,56]. One AIDS patient has been reported in which parkinsonism resolved on HAART alone with normalization of CD4 count [22].

Clozapine has been studied in six patients in an open, rising dose study as a treatment for HIV patients with psychosis and neuroleptic-induced parkinsonism. Patients were withdrawn from their neuroleptic medications at least seven days prior to being placed on clozapine. A significant reduction in psychosis as well as parkinsonism (as measured by the UPDRS motor subsection) was noted, although it was unclear whether parkinsonian signs were decreased by the action of clozapine, withdrawal of neuroleptic drugs or both actions [57].

4. Chorea and ballism

4.1. Epidemiology of chorea/ballism

Choreoathetosis in AIDS was first reported by Navia and coworkers in 1986 [58], the same year Martinez-Martin et al.
described another HIV patient who presented with hemichorea–hemiballism [59]. One year later Nath and coworkers described three other cases [2]. Since then, a growing number of patients with HIV-related choreoathetosis and ballism have been reported. The exact frequency of these disorders is not clearly established. While some studies have reported hemichorea–hemiballism as the most common movement disorder in HIV positive patients [60–62], other reports describe them as the second most frequent movement disorder after parkinsonism [3,21]. Interestingly, hemichorea–hemiballismus is one of the rarest of all movement disorders in patients without HIV infection [63].

4.2. Clinical features of chorea/ballism

The clinical picture of AIDS related hemichorea–hemiballismus does not differ from that in patients without HIV infection. The hyperkinetic movements may affect proximal and/or distal muscles of the extremities and range from ballistic to choreic or choreoathetotic movements. Hemichorea-hemiballism and even generalized chorea may be the initial presenting symptom of AIDS. [64–66].

The involuntary movements typically compromise only one side of the body and the clinical onset is usually acute or subacute [21,59,64,67]. In contrast, generalized chorea is rare in AIDS patients. Gallo et al. reported one case of bilateral choreic and ballistic movements associated with HIV encephalitis [68]. Pardo and coworkers reported a second case of generalized chorea in a patient with HIV encephalitis and neuropsychological symptoms consistent with HAD [65]. Bilateral chorea has also been reported in one patient with bilateral toxoplasma abscesses who was not examined with neuroimaging or autopsy [69].

Facial chorea is extremely uncommon in AIDS patients. Nath et al. published a case with involuntary facial movements preceding the appearance of hemichorea–hemiballism secondary to cerebral toxoplasmosis [67]. Another AIDS patient presented with bucco-lingual and masticatory dyskinesias, in which the facial movements were assumed to be iatrogenic due to noradrenaline and dopamine used for the treatment of hypovolemic shock [62].

4.3. Etiology of chorea/ballism

Most cases of AIDS-related hemichorea–hemiballismus are associated with lesions affecting the contralateral subthalamic nucleus or striatum [2,62,67,70] (Table 1). The majority of cases of chorea-ballism in AIDS reported multiple cerebral lesions rather than a single one. The cerebral structures more commonly affected are the subthalamic nucleus, thalamus, head of the caudate, putamen, globus pallidus, midbrain and internal capsule [64,71,72].

A subthalamic toxoplasmic abscess is the most common cause of hemichorea-hemiballism in AIDS patients [2,58,70]. Some authors suggest that the appearance of hemichorea–hemiballism in AIDS patients is virtually pathognomonic of cerebral toxoplasmosis [58]. However, the presence of hemichorea–hemiballism in patients with cerebral toxoplasmosis is not common, occurring in only 7.4% of cases, which is surprisingly low considering that pathological studies have shown that in 50% of cases toxoplasma abscesses occur in the basal ganglia. The reason for this large discrepancy remains unclear [58,64,70]. Interestingly, movement disorders have not been described in patients with cerebral toxoplasmosis without HIV infection [67]. However, it should be emphasized that acquired cerebral toxoplasmosis was exceptional before the AIDS era. Cases of AIDS-related toxoplasmosis are now relatively numerous and the probability of observing movement disorders has considerably increased [73].

Generalized chorea may be the result of bilateral toxoplasmosis abscesses but may also be associated with HAD [65,68,69]. More rarely, other etiologies have been described, including cryptococcus [61], progressive multifocal leukoencephalopathy and iatrogenic [62].

In Piccolo et al.’s series of 51 sporadic cases of chorea, 5/51 patients had chorea in association with AIDS. Two patients had chorea secondary to toxoplasmosis, with one having a toxoplasma abscess in the contralateral STN and one having basal ganglia toxoplasmosis. One patient had generalized chorea and HIV encephalitis, one had focal chorea after dopamine treatment for meningoencephalitis and one patient had focal chorea secondary to PML. Piccolo et al. concluded that AIDS-related disease should be considered in young patients presenting with chorea without a family history of movement disorders [74].

4.4. Pathophysiology of chorea/ballism

Lee and Marsden in a review of movement disorders arising from lesions of the thalamus and subthalamus conclude that ballism or chorea were convincingly associated with damage to the subthalamic nucleus or its efferent pathways, which removes excitation of the globus pallidus, thus disinhibiting the ventrolateral and ventroanterior thalamic nuclei receiving pallidal projections [75]. The pathogenesis of chorea–ballism in HIV-related opportunistic lesions appears to be due to the same mechanisms of chorea generation due to other destructive lesions of the subthalamus.

4.5. Treatment of chorea/ballism

The management of patients with HIV-related hemichorea–hemiballism includes the diagnosis and treatment of opportunistic infections, the symptomatic treatment of the movement disorder and the use of HAART [14]. In some cases, antitoxoplasmosis therapy consisting of sulfadiazine and pyrimethamine was followed by a marked improvement or even resolution of the involuntary movements [62,64,70], although other authors found that clinical
response to antitoxoplasmosis therapy was poor, with little or no improvement of the movement disorder [58,72]. Nath and coworkers suggested that the underlying HIV infection may play a role in the persistence of the movement disorder despite abscess resolution after antitoxoplasmosis therapy [67].

Symptomatic control of the hyperkinetic movements is sometimes necessary. Chorea may respond to antidiopaminergic agents such as dopamine receptor blockers, and presynaptic dopamine depleters like tetrabenazine [68,76] Occasional cases may be resistant to pharmacological treatments [67]. In generalized chorea associated with HIV encephalitis, treatment with antiretroviral and antidiopaminergic drugs has been reported by Gallo et al. as unsuccessful in controlling the movements [68]. However, Pardo et al. have reported one patient with bilateral chorea associated with HIV dementia complex who had an excellent response to antiretroviral therapy [65].

5. Myoclonus

5.1. Epidemiology of myoclonus

Myoclonus is a rarely reported movement disorder in AIDS patients (Table 1). Both segmental and generalized myoclonus have been described in AIDS patients. In de Mattos et al.’s series of 2460 HIV positive inpatients, four patients had myoclonus, two with spinal myoclonus and two with generalized myoclonus [21].

5.2. Clinical features and etiology of myoclonus

Nath et al. described two patients with segmental myoclonus associated with other movement disorders and neurologic abnormalities [2]. No clear correlation was observed between the clinical signs and lesions observed on brain imaging studies. Myoclonus was the first manifestation of HIV infection in one patient and occurred 17 months before AIDS was documented. Lubetzki et al. described a single case of axial myoclonus causing flexion of the neck, trunk and lower extremities, in which no structural lesions were found. In this patient, the myoclonus was an early manifestation of CNS HIV infection [77].

Three cases of generalized myoclonus reported by Maher et al. were associated with HAD. One patient had a cerebral toxoplasmosis abscess. The myoclonus was elicited by sudden auditory stimuli, resembling a startle response, and was a late feature of the disease, occurring and persisting several months before death. The appearance of myoclonic dementia had a poor prognosis, leading to death within three months after the onset of myoclonus [6].

In their series of 2460 HIV positive inpatients de Mattos et al. reported two cases of spinal myoclonus. One patient had radiculomyelopathy most likely due to Mycobacterium tuberculosis and in the second case it was thought that the myoclonus was likely due to dorsal herpes zoster. Two cases of generalized myoclonus were also reported, one due to toxoplasmosis and one due to HAD [21]. In another series of 1086 AIDS patients, de Mattos et al. described one patient who presented with a progressive tuberculous radiculomyelopathy and myoclonic jerks in the lower limbs, which were presumed to be spinal in origin since it was seen only in the lower limbs and EEG was normal [3].

One patient presented with arm and shoulder segmental myoclonus preceding the onset of herpes zoster radiculitis, which remitted promptly with antiviral treatment [78]. Thomas and Borg reported a patient with segmental myoclonus associated with triphasic waves on EEG, both of which resolved with zidovudine therapy [79].

Progressive myoclonic ataxia has been described as the presenting symptom in an AIDS patient. MRI showed bilateral, symmetrical lesions in the red nucleus, subthalamus, thalamus, lenticular nuclei, and primary motor cortex which were confirmed neuropathologically to be those of progressive multifocal leukoencephalopathy [80].

5.3. Pathophysiology of myoclonus

In a series of cases of generalized myoclonus seen with HAD, the myoclonus was physiologically associated with predominantly subcortical mechanisms. All patients had prominent subcortical symptoms, and one patient had pathological confirmation of brainstem and bilateral nucleus reticularis gigantocellularis and nucleus reticularis pontis caudalis involvement [81]. However, inferences about anatomical localization were limited by the diffuse nature of the pathologic condition. EEG showed inconsistent evoked response or absent cortical paroxysmal activity. Maher et al. suggest that the generalized myoclonus seen in their series of three patients may have been subcortical in origin, as a sudden auditory stimulus evoked generalized myoclonus in two patients, suggesting a brainstem origin involving the auditory-induced startle response pathway [6, 82]. The possibility of cortically induced myoclonus is not excluded, as patients with HIV infection and myoclonic epilepsy have been reported [79].

The mechanism of spinal myoclonus is unknown. Experimental, clinical and pathologic evidence support Bradshaw’s theory of intercalated neurons within the posterior horn. Increased gamma motor neuron activity has also been proposed but anterior horn cells are unlikely to be involved in isolation, since some patients have myoclonus without paralysis and others have myoclonus affected by sensory stimuli [83,84]. Koppel and Daras hypothesize in their patient with segmental myoclonus preceding herpes zoster radiculitis a localized viral myelitis involved intercalated neurons and sensory pathways contralateral to the skin eruption [78].

Myoclonic ataxia as a presentation of PML lesions in bilateral red nuclei, subthalamus, thalamus, lenticular nuclei
and primary motor cortices suggests a role of the dentato-rubral-thalamo-cortical tract in the pathogenesis of progressive myoclonic ataxia [80].

5.4. Treatment of myoclonus

In a series of three patients with generalized myoclonus and HAD, Maher et al. noted only one patient with Toxoplasma gondii abscess, whose myoclonus did not respond to antimicrobial treatment, although it partially responded to treatment with clonazepam [6]. In one patient with tuberculous radiculomyelopathy associated with spinal myoclonus, treatment with anti-tuberculosis medications resulted in mild improvement of the paraplegia and myoclonus [3]. Myoclonus remitted promptly with antiviral treatment with acyclovir in a patient with segmental myoclonus preceding herpes zoster radiculitis [78]. In one patient with myoclonic encephalopathy associated with HAD and sharp wave activity on EEG, dramatic neurologic improvement as well as EEG normalization occurred upon treatment with intravenous and then oral zidovudine [79].

6. Dystonia

6.1. Epidemiology of dystonia

Dystonia has rarely been reported in patients with AIDS. However, generalized, segmental, and focal dystonia have been described in AIDS patients (Table 1).

6.2. Clinical features and etiology of dystonia

De Mattos and coworkers in their review of 2460 HIV positive patients reported only one case of hemidystonia which was due to toxoplasmosis of the contralateral basal ganglia [21]. A case of postural tremor associated with dystonia and a case of paroxysmal dystonia were described among seven AIDS patients with movement disorders. The first patient presented with dystonia in both hands and MRI showed small lesions in the left thalamus and posterior internal capsule, which did not correlate with the movement disorder. The second patient presented with acute paroxysmal dystonia with a left frontal lesion on MRI. No information was given with regard to infectious agents [2]. Abbruzzese et al. reported a patient with generalized dystonia involving both axial and segmental muscles. A CT scan revealed bilateral, symmetrical lucencies in the putaminal region [7]. A patient with left arm and hand focal dystonia due to a toxoplasmosis abscess in the right lenticular nucleus and thalamus has been reported [85].

Vielhauer et al. reported one AIDS patient with disseminated cytomegalovirus (CMV) infection and bilateral thrombosis of the internal jugular veins presenting with spasmodic torticollis and an extrapyramidal syndrome. The authors suggest that the dystonia was caused by the vein thrombosis rather than the CMV infection, due to rapid resolution of the torticollis with anticoagulation treatment. The patient’s other extrapyramidal signs resolved with anticytomegalovirus medications [86]. AIDS patients treated with dopamine receptor antagonists appear to be particularly susceptible to developing an acute onset medication-induced dystonia (and/or parkinsonism) [36,87]. Factor et al. reported the first pathological description of a patient with ADC who developed an acute onset dystonia and rigidity after a brief trial of low dose neuroleptic therapy, which was persistent. Pathological examination revealed a generalized encephalitis with substantial neuronal loss in the medial and lateral globus pallidus [38].

6.3. Pathophysiology of dystonia

It has been hypothesized that the increased susceptibility of AIDS patients to develop acute dystonia to low doses of dopamine receptor antagonist medications is probably related to direct invasion of the basal ganglia by the HIV virus and a secondary alteration in dopaminergic mechanisms [36]. Factor et al. suggest in their case report of one HAD patient who developed persistent neuroleptic-induced dystonia that the severe neuronal loss seen in his globus pallidus increased his vulnerability to developing extrapyramidal side effects. They suggest that dopamine related changes are already present pathologically in patients who are prone to develop medication-induced dystonia [38]. However, extrapyramidal reactions are also described in patients with no apparent neurologic disorder [87].

6.4. Treatment of dystonia

In de Mattos’ case of hemidystonia due to basal ganglia toxoplasmosis, treatment with sulfadiazine and pyrimethamine improved the lesions radiographically but did not change the dystonia [21]. Factor et al. described one patient with HAD with persistent neuroleptic-induced dystonia, in which treatment with trihexyphenidyl, diphenhydramine, loresal and carbidopa/levodopa failed to alleviate the dystonia. The patient was then treated with electroconvulsive therapy for paranoid delusions and depression which reduced the dystonia for several hours [38]. In one patient with generalized dystonia associated with bilateral striatal lucencies on CT scan, slight improvement of the dystonia was noted with high dose anticholinergic treatment [7]. Given the increased risk of AIDS patients to develop dystonia on dopamine receptor antagonist medications, extreme caution should be used when prescribing such medications. If antiemetic medications are required, non-dopamine antagonists or peripheral acting dopamine antagonists are preferred.
6.5. Paroxysmal Dyskinesias

Paroxysmal dyskinesias, a rare movement disorder which presents with dystonic or choreoathetotic movements that occur suddenly and transiently, with complete recovery between attacks, have been described in two case reports of AIDS patients (Table 1). Nath et al. described an AIDS patient who presented with paroxysmal nonkinesigenic dystonia with an MRI showing a lesion in the left frontal region [2]. Mirsattari et al. reported six AIDS patients who presented with paroxysmal dyskinesias. Histopathologic analysis of one patient revealed severe HIV encephalitis with intense astrogliosis and loss of calbindin-positive neurons in the subcortical gray matter. It is hypothesized that infection of the basal ganglia by HIV may lead to calcium metabolism dysregulation, causing paroxysmal dyskinesias. Patients with paroxysmal kinesigenic dyskinesias improved with benzodiazepine treatment, while only one patient with paroxysmal non-kinesigenic dyskinesias improved with benzodiazepine treatment [10].

7. Conclusion

Patients with HIV infection, particularly patients with HAD, may manifest a variety of movement disorders. Recognition of the movement disorder in these patients is important since it may represent the initial presentation of HIV infection. Alternatively, the movement disorder may indicate the presence of an underlying mass lesion or CNS infection related to AIDS. It is also important to be cognizant of the heightened sensitivity of AIDS patients to the potential extrapyramidal side effects of dopamine receptor antagonist medications. Proper evaluation of AIDS patients with movement disorders includes looking for underlying treatable AIDS-related illnesses, and ascertaining exposure to medications which can provoke an iatrogenic movement disorder. Current data suggest that dopaminergic dysfunction plays a critical role in the pathogenesis of HIV-related CNS manifestations. Available treatments for AIDS-related movement disorders have had variable success. Dopamine agonists have shown promise in the treatment of motor dysfunction in a very limited number of pediatric patients. In adults, experience with dopaminergic treatment has been limited to only anecdotal reports. In addition, any motor improvement afforded by dopaminergic medications must be weighed against the potential risk of inducing cognitive side effects in patients with AIDS dementia.

Much of the current available data on movement disorders in AIDS patients is retrospective in nature. To further advance our knowledge of movement disorders and AIDS, prospective studies of HIV patients with evaluations by movement disorder specialists should be done, with detailed clinico-anatomic correlations. Future avenues of treatment should focus on the aggressive control of HIV infection with HAART.

Finally, it should be noted that HAART has resulted in improved survival times with HIV infection [88]. Higher incidence of comorbid medical conditions is likely to emerge with aging of the HIV-infected population [89]. It may be predicted that the incidence of comorbid neurodegenerative conditions such as parkinsonism will also rise over time, although surveys regarding the incidence of parkinsonism in elderly HIV cohorts are lacking. There is a need for controlled clinical trials to assess the effect of HAART on the incidence and manifestations of neurodegenerative conditions such as parkinsonism in the increasingly frequent older HIV population.

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