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Review

Primary neurological manifestations of HIV in children

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Abstract

Human immunodeficiency virus type 1 (HIV-1) causes various diseases in different age groups. Neurological manifestations of HIV are common and add to morbidity and mortality. It was previously thought that the central nervous system (CNS) was involved only in the advanced stages of the disease. However, recent evidence supports pathological involvement of the CNS from initial viral entry. Some of the CNS manifestations in children share similarities to neurologic disorders of HIV-infected adult patients, while others are unique to the pediatric population. Many HIV-related neurologic complications seen in adults are rarely encountered in children with AIDS and vice versa. However, with recent advances in the treatment, more HIV-infected children are surviving into adulthood. A systematic review of the available literature was performed to study the manifestations, causes, outcomes, and treatment of primary neurologic disorders in children with HIV. Online databases (Ovid Medline, Embase and PubMed), websites from the World Health Organization, commercial search engines, including Google, and chapters on HIV in standard textbooks of pediatrics and medicine were reviewed.

HIV-associated neurological syndromes can be classified into four types: primary HIV neurological diseases, treatment-related neurological diseases, adverse neurological effects of antiretroviral therapy and secondary/opportunistic neurological illness. These conditions are not mutually exclusive and may co-exist in a given patient. This narrative review will focus mainly on the primary neurological manifestations of HIV in children.

Key words: HIV; neurological; children; peripheral neuropathy; myopathy; spinal cord.

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Introduction

Human immunodeficiency virus -1 (HIV-1) is an RNA retrovirus and belongs to the Lentivirus subfamily of non-oncogenic retroviruses [1]. Lentiviruses have long incubation periods and can evade immune clearance, causing persistent infection and chronic disease [2]. Of the estimated 38 million people living with HIV worldwide in 2020, 2.78 million were children aged 0–19 years [3]. Although the progress in HIV management has been promising, children continue to be affected by the epidemic. Combined antiretroviral therapy (cART) has significantly impacted the course of the disease in children by reducing mortality [4]. However, chronic co-morbidities continue to affect the health and well-being of HIV-infected children. Of these, HIV-associated neurological syndromes significantly impact the quality of life [4]. HIV can primarily or secondarily affect all parts of the nervous system. HIV-associated neurological syndromes can be classified as:

1. Primary HIV neurological disease (in which HIV is both necessary and sufficient to cause the illness)
2. Treatment-related neurological disease (immune reconstitution inflammatory syndrome or IRIS)
3. Adverse neurological effects of antiretroviral therapy (ART).
4. Secondary or opportunistic neurological disease (in which HIV interacts with other pathogens resulting in opportunistic infections)
5. Tumours (Kaposi sarcoma)

In this review, we will briefly discuss the neuropathogenesis of HIV and focus on the primary neurological manifestations of HIV in children.

Search methods

A literature review was performed to identify data on the neuropathogenesis, manifestations, causes, outcomes, and treatment of neurologic disorders in children with HIV. Online databases (Ovid Medline, Embase and PubMed) were searched to identify relevant articles published in English using

combinations of '(child or children or adolescent or infant)' AND, '(neurology or nervous system diseases or neurological impairment) AND (AIDS or acquired immunodeficiency syndrome or human immunodeficiency virus or HIV). Websites from the World Health Organization were scanned for further references. The abstracts of any articles identified in this search strategy were screened for relevance, and electronic copies of the full text were obtained for all relevant articles. References from each relevant article were scanned for further relevant articles, and a snowball search was performed. Commercial search engines, including Google, were also used to check for missing publications. We also reviewed chapters on HIV in the standard textbooks of pediatrics and medicine.

Neuropathogenesis of HIV infection

The majority of the neurological effects of HIV arise either from the direct toxicity of viral proteins or from the indirect neurotoxic effects of chronic activation of immune cells in the central nervous system (CNS) [4-7]. The chronic release of inflammatory cytokines and other toxic substances like reactive oxygen species contributes to a sustained inflammatory environment and subsequent CNS dysfunction. Though early CNS infection is usually asymptomatic, cerebrospinal fluid (CSF) and imaging studies can detect abnormalities even during the "asymptomatic" period that precedes neurological events [8]. To enter the CNS, HIV has to cross the blood-brain barrier (BBB). Various hypotheses have been formulated to explain the mechanisms by which HIV crosses the BBB. In the 'Trojan horse' hypothesis, the virus crosses the BBB in infected cells such as T lymphocytes or monocytes, especially CD14+ and CD16+ monocytes [4]. Other contributory mechanisms involve disruption of the BBB by proinflammatory cytokines or by alteration of the expression of endothelial cell tight junction proteins by the viral protein 'Tat' [4,9]. Some data have also suggested that free viral particles may cross the BBB, although this remains controversial [4,9,10]. Significant reservoirs of the virus in the CNS are the microglial cells and perivascular macrophages, which express the CD4 and CCR5 receptors [4]. Astrocytes and oligodendrocytes are suboptimal reservoirs for HIV as they don't express CD4/CCR5 receptors [4,9,10]. However, they do play a significant role in the neurotoxic effects of HIV. Neurons express receptors that make them susceptible to damage by viral proteins, cytokines, and immune cell secretions [11]. Other factors include the unique immune environment of the CNS being more permissive to viral replication and combined antiretroviral therapy (cART) not being able to cross the BBB very effectively [4,9-11]. All these factors together contribute to the development of neurologic dysfunction in HIV-infected people.

Difference between neuropathogenesis in HIV-infected children and adults

The CNS of children seems to be more vulnerable to the effects of HIV than that of adults. This is perhaps because the pediatric CNS is still developing and immature and contains less differentiated cell types. This could also be responsible for the rapid progression of HIV infection in children, particularly infants [12-14]. According to Sharer *et al*., there are significant differences in the CNS of HIV-infected children compared with HIV-infected adults. In children, there is increased inflammation and localization of multinucleated giant cells (MGC) in the cerebral cortex. These MGCs are syncytial cells of resident microglia fusing with invading macrophages and glial-microglial nodules [12]. In contrast, HIV-infected adults show

Table 1. Comparison of neurologic manifestations in HIV- infected adults versus children.

Adults	Children
Horizontally acquired primary infection	Vertically acquired primary infection
Long latency from primary infection to symptoms	Rapidity to symptoms after primary infection
Deterioration of a mature CNS	Impairment of growth of an immature CNS
CNS OI frequent; Usually associated with immune deficiency	CNS OI infrequent
PNS involved often	PNS rarely involved
CSF non-specific for ADC	CSF non-specific for progressive encephalopathy
Aseptic meningitis at time of seroconversion	Aseptic meningitis ill-defined
Seizures common	Seizures infrequent
Psychiatric complications common	Neurobehavioral changes common
Brain "atrophy"	Impaired brain growth
Motor deterioration/cognitive decline/dementia	Progressive motor dysfunction/neurodevelopmental decline is usually associated with immune deficiency

CNS: central nervous system; OI: opportunistic infections; PNS: peripheral nervous system; CSF: cerebrospinal fluid; ADC: Acquired immunodeficiency syndrome dementia complex.

increased perivascular brown pigment and significant white matter changes. White matter astrocytosis is noted in children and, although not specific for HIV-1 brain infection, is felt to be a pathognomonic histologic marker [12-14]. Recent studies in adults have shown increasingly convincing evidence of a reduced neuronal population secondary to neuronal dysfunction/destruction correlating with the AIDS dementia complex (ADC) [13]. However, neuronal destruction has rarely been reported in children, but other pathologic changes in the grey matter have been noted [13]. Vacuolar myelopathy is a postmortem finding in up to 30% of adults but has been rarely observed in children and is primarily associated with the reactivation of opportunistic infections, such as cytomegalovirus and measles [12,15]. Delayed myelination of the corticospinal tracts may be distinctive in pediatric patients, although the mechanism for such a process has not been defined [12]. The differences in the neurologic manifestations of HIV-infected adults and children have been summarised in Table 1 [13].

Primary neurological manifestations of HIV

We have classified the primary neurological manifestations of HIV in children into three sub-categories based on the part of the nervous system affected: the brain, the spinal cord, and the peripheral nervous system (Table 2).

Brain

Neurocognitive complications of HIV

Neurological changes in HIV occur across three subcortical domains: cognitive (manifesting as deficits in memory, concentration, comprehension, or executive planning); behavioral/affective (leading to apathy, depression, or agitation); and motor (gait unsteadiness, decreased coordination, tremor). In horizontally HIV-infected adults, the virus affects the brain after it fully develops. In contrast, in perinatal transmission, the virus affects the brain during a crucial time of CNS development. Perinatal transmission of HIV infection can occur during pregnancy, delivery, or breastfeeding. Maternal HIV has been associated with an increased risk of low-birthweight and small-for-gestational-age infants, with an increased risk of mortality and developmental delay [16,17]. Before highly active antiretroviral therapy (HAART) was introduced, encephalopathy was reported in 35% to 50% of children diagnosed with AIDS in the United States. However, with the routine use of ART in children, the cumulative incidence of progressive encephalopathy has decreased to less than 2% [18]. Before the widespread use of ART, symptomatic CNS HIV-1 disease was seen to have a trimodal evolution [19]. The first peak occurred in infancy, the second in childhood and the third smaller peak in adolescence.

Clinical features

Impaired brain growth: In children younger than two years of age, impaired brain growth manifests as decelerating head growth or acquired microcephaly. In older children, it manifests as cortical atrophy on neuroimaging [19].

Progressive pyramidal tract signs: There is a loss of motor milestones. The child who was earlier able to walk independently has a change in gait, begins to toe-walk and is later unable to stand or take steps. These corticospinal signs are generally progressive and result in spastic paraparesis or quadriparesis with or without pseudobulbar signs. Cerebellar signs and movement disorders like rigidity, dystonic posturing, and tremors have also been described [19].

Developmental delay and cognitive impairment: Various studies have shown that HIV-infected children have significantly poorer performance on early motor and cognitive development measures than uninfected children. Effects are accentuated by co-morbid illnesses, poor nutrition, and adverse living conditions [20-22]. CNS manifestations range from loss of previously acquired developmental milestones (like language and social adaptive skills) to the more severe form, i.e., HIV encephalopathy. In HIV-infected older children, CNS involvement initially manifests as a decline in academic performance. Other signs described

Table 2. List of primary neurological manifestation of HIV in children.

Brain	Spinal cord	Peripheral nervous system
Neurocognitive complications of Human immunodeficiency virus [HIV]	Sub-acute myelopathies - Vacuolar myelopathy	Distal symmetric polyneuropathies
Acute disseminated encephalomyelitis (ADEM)	Acute myelopathies	Mononeuritis multiplex
HIV associated cerebrovascular complications		HIV-related acute inflammatory demyelinating polyneuropathy
Epilepsy		Mitochondrial toxicity: a syndrome that may mimic Guillain-Barre syndrome

are social withdrawal, behavioral problems, emotional lability, visuospatial, motor integration, attention and memory deficits, and conduct and language disorders [23]. Older children and adolescents may develop HIV dementia like that seen in adults [24]. These can result in profound functional impairment in school-going children infected with HIV.

HIV-associated neurocognitive disorder (HAND): There are well-defined criteria for the diagnosis of HIV encephalopathy and "slow progression" in HIV-positive children. However, little is known about the cognitive function of children stable on ART and not meeting the diagnostic criteria for encephalopathy or slow progression [25,26]. In contrast, adult literature on HIV-related CNS damage supports a spectrum of disorders referred to as HAND [27]. The clinical presentation of HAND varies from asymptomatic or minor neurocognitive impairment to severe dementia and HIV encephalopathy. The diagnosis is made in HIV-positive patients with cognitive impairment after ruling out confounding conditions (opportunistic infections of the CNS, neurosyphilis, substance abuse, delirium, toxic-metabolic disorders, psychiatric disease, and age-related dementias) [25-27]. The Frascati criteria, developed in 2007, are commonly used to diagnose HAND [28]. Due to marked improvement in HIV treatment, many children are now surviving into young adulthood. Since neurocognitive impairment can harm children's ability to function, clinicians need to be able to identify and manage these impairments. Hence, similar spectrum criteria need to be developed for pediatric HIV.

Hoare *et al*. applied the HAND criteria used in HIV-infected adults in a cohort of HIV-infected youth (aged 6–16 years) to establish whether they can detect neurocognitive disorders in HIV-infected youth. They found that the HAND criteria designed for adults could identify youth with significant functional cognitive impairments who did not fit the criteria for HIV encephalopathy and would not have been identified otherwise [29]. This has important clinical implications in the management of HIV-infected youth.

Laboratory evaluation

Cerebrospinal fluid (CSF): CSF parameters in children with HIV-1 are usually normal unless there is an opportunistic infection. CSF examination may show mild pleocytosis, mainly lymphocytosis and raised CSF protein which is seldom more than 100 mg/dL. Viral load in the CSF is not routinely tested for diagnosis since there is a significant overlap between children with and without encephalopathy. Levels above 10^6 copies/mm^3 have been demonstrated with HIV dementia [29-33].

Radiological findings associated with progressive HIV encephalopathy (HIVE)

The most common finding on neuroimaging is diffuse cortical atrophy with apparent enlargement of the ventricles and subarachnoid space. Focal demyelination of the centrum semi-ovale or frontoparietal white matter may be seen. Frontal lobe or basal ganglia calcification is seen in the late stages. Magnetic resonance imaging (MRI) is the imaging modality of choice because of its greater sensitivity in picking up demyelination [19,30].

Antiretroviral drugs and neurodevelopment

Since the introduction of interventions to prevent mother-to-child transmission, variable improvement in the mean developmental scores in HIV-infected infants exposed to a protease inhibitor-based HAART regimen in utero has been reported [31]. Shanbhag *et al*. found that the prevalence of static or progressive encephalopathy declined from 40.7% in children born before 1996 to 18.2% in children born after 1996, i.e., after ART was introduced in pediatric HIV practice [32]. Infants started on treatment before 12 weeks of age demonstrated better, but still subnormal, mean locomotor scores than those with delayed treatment. Two multicenter studies documented a progressive decline in the incidence of HIVE and microcephaly after increased access to ART [33,34]. ART administered to children with established HIVE prevents the progression of the neurologic stigmata, limits the severity of the neurologic sequelae, and may affect the partial reversal of the neurologic features of HIVE.

Timing of ART is critical for optimizing neurodevelopment and cognitive performance. Early ART initiation before three months of age is associated with a significantly better neurodevelopmental outcome. Laughton *et al*. found that when ART was begun in asymptomatic or mildly symptomatic HIV-infected infants with a median age of 8.4 weeks, their neurodevelopment at a median age of 11 months was significantly better than if ART initiation was deferred until a median age of 31.4 weeks [35]. Subtle deficits in higher cognitive functioning (poorer memory and language development) and behavior exist in school-aged children with only limited improvement after initiation of antiretroviral therapy [36]. AIDS-defining conditions before ART initiation are associated with

lower cognitive scores in perinatally infected children and adolescents [37,38].

Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is a para-infectious disorder usually seen following viral infections and vaccines. The association between ADEM and primary HIV infection is rare [39]. An extensive literature search revealed at least three pediatric cases of ADEM in HIV infection. Of these three cases, only one had ADEM associated with primary HIV infection. Patra *et al.* reported a 10-year-old HIV-infected child presenting with monoparesis and progressing to triplegia over four weeks [40]. Serological IgM titers for *Toxoplasma gondii*, *Treponema pallidum*, Cytomegalovirus and the hepatitis B, rubella and herpes simplex and hepatitis C viruses, Mantoux test, and the hepatitis B surface antigen were negative. The child received methylprednisolone and intravenous immunoglobulins but deteriorated and died before ART could be initiated. The prognosis of ADEM in children appears guarded as compared to adults. It is unknown whether ADEM is due to a direct invasion of HIV into the CNS or is part of an immune-mediated mechanism leading to an inflammatory response against myelin in the CNS.

HIV-associated cerebrovascular complications

The frequency of cerebrovascular complications in children with AIDS is 1.3–2.6 %, although a higher prevalence (4–36%) of cerebral ischaemic lesions is reported during autopsy [41-44]. The complications include either ischemic or hemorrhagic strokes or subarachnoid bleeds due to aneurysm rupture. Park *et al*., in a longitudinal study of neurological complications of HIV, found four of 68 children to have clinical or neuroradiological evidence of stroke [44]. An autopsy was done on 18 of 25 patients, including three with clinical stroke. Four patients showed intracerebral hemorrhage, six showed non-hemorrhagic infarcts, one child had an arteriopathy affecting the meningo-cerebral arteries, and one had aneurysmal dilatation of the circle of Willis arteries. Patsalides *et al*. studied the prevalence and the neuroradiologic manifestations of cerebrovascular complications in children infected with HIV [45]. They found that these complications were associated with end-stage HIV disease since all but one patient had evidence of severe immune suppression when cerebrovascular abnormalities were detected.

The mechanism by which arterial damage leads to aneurysmal dilatation is not well-understood. Park *et al*. identified HIV viral antigen in the intima of affected arteries using monoclonal antibodies to glycoprotein (gp) [41]. They suggested that HIV infection of the parenchymal and leptomeningeal vessels may be responsible for vascular complications in children with AIDS [44]. Husson *et al*. found that cerebral aneurysms occurred in children during significant HIV replication, as indicated by high serum p24 antigen levels [46]. Other investigators have suggested that other viral agents acting alone or in synergy with HIV may be involved in the pathogenesis of arteriopathy in pediatric HIV infection. Dubrovsky *et al.* reported a history of varicella-zoster infection or elevated varicella-zoster virus antibody titers in HIV-infected children with cerebral aneurysms [47]. Patsalides *et al*. found that most of the infarctions in their study occurred in vascular territories harbouring the aneurysms, suggesting that the infarctions were causally related to the aneurysms [45]. They hypothesized that the orifice of these vessels was compromised or occluded by distortion of the wall anatomy of the ectatic parent artery or by mural thrombi. The HIV-infected pediatric population has a higher incidence of fusiform aneurysms than the general population [45]. These aneurysms are often multiple (57%) compared to non-HIV-infected children, whose frequency of multiple aneurysms is only 2% [45].

Koh *et al.* found two of 37 children with an ischemic cerebrovascular accident to have decreased levels of protein C and five with reduced levels of protein S [48]. Acquired protein C and protein S deficiencies in HIV-infected children could be significant risk factors for thrombo-embolic complications. Hemorrhagic complications due to thrombocytopenia have been reported in pediatric patients with AIDS; the clinical presentation is with focal neurological deficits consistent with a diagnosis of stroke [44]. Rakhmanina *et al.* described a case of HIV-thrombotic thrombocytopenic purpura (TTP) in a 16-year-old female with perinatally acquired HIV infection [49]. The patient presented with an acute hemorrhagic stroke with severe thrombocytopenia and microangiopathic hemolytic anemia. Investigations showed a decrease in plasma ADAMTS13 activity (< 5%) without detectable inhibitory antibodies confirming HIV-TTP diagnosis. ART was started, and plasma exchange was done. The patient responded with a marked decrease in the HIV-RNA viral load and recovery of the platelet count. Other HIV-related causes of stroke include opportunistic infections like tuberculous meningitis, varicella-zoster virus vasculitis and neoplasms such as CNS lymphoma [50]. The

imaging modality of choice is magnetic resonance imaging [MRI] or computed tomography (CT) angiography.

Epilepsy

Epilepsy in children with HIV-1 infection may be related directly to viral damage or may be secondary to acquired pathology. The prevalence ranges between 7.6% and 14% [26]. There are major drug-drug and drug-disease interaction challenges while managing epilepsy in HIV- infected children. Phenytoin, phenobarbitone, and carbamazepine increase the cytochrome P450 complex's metabolic activity; concurrent use with protease inhibitors (PI) may result in subtherapeutic ART levels and treatment failure, as well as potential resistance. Sodium valproate and lamotrigine are recommended as first-line agents, with levetiracetam as an alternative drug [26].

Spinal cord disorders

Sub-acute myelopathies - vacuolar myelopathy (VM)

Spinal cord involvement has been commonly described in autopsies of adults with HIV infection, but it is rare in children [51]. Vacuolar myelopathy (VM) is the type of myelopathy most associated with HIV-1 in the developed world. It is a slowly progressive painless spastic paraparesis with sensory ataxia and neurogenic bladder. It is characterized by prominent vacuolar changes in the ascending and descending tracts that mainly affect the thoracic spinal cord [52]. Though VM has been identified pathologically in almost 50% of cases at autopsy in adults, it is symptomatic in only 5–10% of patients with AIDS [53]. Vacuolar myelopathy occurs in children with HIV but less frequently than in adults. Sharer *et al.* did an autopsy study on the spinal cords of children who had died of HIV infection [54]. They found two cases of VM among 18 cords examined. One was in a 30-month-old boy with concomitant measles virus in the spinal cord. The other was a nine-year-old girl with severe HIV infection of the spinal cord. Bhigjee *et al.* from South Africa reported a three-year-old girl with an infantile onset of HIV-associated myelopathy [55]. The baby was born by normal vaginal delivery to an HIV-positive mother, and infection occurred possibly in-utero or during delivery. The mother had noticed delayed fetal movements. The child had delayed motor development: she crawled at 16 months and walked at 30 months but had frequent falls. Her mental state was normal. Spastic paraparesis was present on examination; pinprick sensation was normal. CT myelogram was normal.

Acute myelopathies

Other causes of myelopathy in HIV/AIDS include opportunistic infections, neoplasms, vascular lesions and metabolic disease [56]. In developing regions, opportunistic infections leading to acute myelopathies are more commonly encountered, with VM being infrequently reported.

Peripheral nervous system involvement

Distal symmetric polyneuropathies

Distal symmetric polyneuropathies include polyneuropathy due to the virus and toxic antiretroviral neuropathy, the clinical features of which are difficult to distinguish. Peripheral neuropathy is a recognized side effect in adult patients on ART and is particularly associated with using nucleoside reverse transcriptase inhibitors. Peters *et al.* studied HIV-infected children on ART in South Africa using a neuropathy disability score and neuropathy symptom score and found a prevalence of 24% [57]. As in most resource-poor countries, first-line pediatric ART regimes in these children included nucleoside reverse-transcriptase inhibitors. Araujo *et al*. found the prevalence of distal sensory polyneuropathy to be 34% in HIV-infected children in Brazil, whereas Esteban *et al.* from Peru found a prevalence of only 13% [58,59]. The Peruvian study used nerve conduction studies in addition to symptoms and signs to define peripheral neuropathy. Sankhyan *et al*. from India found a prevalence of 10% of distal sensory polyneuropathy in children receiving a stavudine-based combination ART for more than three months [60].

Clinical features

Distal paresthesias and/or pain plus diminished ankle jerks, and/or decreased vibration sense are the most common symptoms in children. The symptoms are typically bilateral and of gradual onset. Nerve-conduction velocities commonly show an axonal, length-dependent, sensory polyneuropathy. The diagnostic approach to a patient with suspected HIV-sensory neuropathy should include a careful history of antiretroviral therapies and address other possible causes of neuropathy, especially other toxic drugs, compression or entrapment neuropathies [58-60].

Mononeuritis multiplex

Mononeuritis multiplex has been described in adults with symptomatic HIV-1 infection. Accurate incidence estimates are not available, and its pathogenesis is poorly understood. It presents as multifocal or asymmetric sensory and motor deficits in

the distribution of peripheral nerves or spinal roots. Deep tendon reflexes mediated by the affected nerves are diminished or absent, but diffuse areflexia does not occur [61]. Reports in children are few. Sugimoto *et al*. reported a 34-year-old man who presented with gait disturbance, left foot drop, low-grade fever and diarrhea [62]. The CSF obtained on admission showed pleocytosis (30/μL) and increased protein. The motor nerve conduction velocities (MCV) of the left peroneal and tibial nerves were slow, but the right peroneal and tibial MCVs were within normal limits. A test for HIV antibody was positive. The Western blot was positive with bands of gp160 and p24, confirming HIV infection. They suggested that acute HIV infection should be included in the differential diagnosis of mononeuritis multiplex.

HIV-related acute inflammatory demyelinating polyneuropathy or Guillain-Barre syndrome (GBS)

HIV-1 associated Guillain-Barre syndrome (HGBS) is an ascending progressive polyradiculoneuropathy described throughout the viral disease and occasionally in severely immunocompromised subjects in the context of the immune reconstitution inflammatory syndrome. Cornblath *et al*. reported nine adults with HIV infection and inflammatory demyelinating polyneuropathies (IDP) [63]. All presented with progressive weakness. Six had chronic IDP, and three had Guillain-Barré syndrome. The results of nerve conduction studies were characteristic of demyelination. Nerve biopsies revealed intense inflammatory cell infiltrates and macrophage-mediated demyelination. The patients recovered either spontaneously or following treatment with corticosteroids or plasmapheresis. The authors found therapy with either prednisone or plasmapheresis was followed by clinical improvement; and suggested that the pathogenesis was immune-mediated. They also suggested plasmapheresis should be used as initial therapy in such patients as it was not likely to depress cell-mediated immunity further.

In 1991, Raphael *et al.* from Baltimore, USA, described a 5-year, 11-month-old Hispanic boy with symptomatic HIV infection and acute demyelinating polyneuropathy [64]. The child presented with a four-day history of limping, stumbling and pain in the right calf. Over the next three days, the child developed progressive weakness in the lower limbs with areflexia, ascending further over the next 24 hours to involve the upper limbs. Facial diplegia and diminished corneal and gag reflexes were also present. CSF examination on the second hospital day showed one lymphocyte with normal protein and glucose. In 2005, Wilmshurst *et al.* from Cape Town, South Africa, described a 2.25-year-old boy with HIV infection with a similar clinical presentation [65].

Mitochondrial toxicity: a syndrome that may mimic Guillain-Barre syndrome

Falco *et al*. described 12 adults with HIV infection who developed severe lactic acidosis while on nucleoside-analogue reverse-transcriptase inhibitors [66]. Three of their patients also developed severe axonal neuropathy of sub-acute onset. Though the pathophysiology is not entirely understood, lactic acidosis suggests acute mitochondrial toxicity. Rosso *et al*. subsequently described severe fatal lactic acidosis, rapid neuromuscular weakness, and respiratory failure mimicking Guillain-Barre syndrome in a 17-year-old [67]. The child was on ART with stavudine, didanosine, tenofovir and amprenavir, suggesting that any patient presenting with a Guillain-Barre syndrome-like picture should be tested for lactic acidosis and evaluated with electromyography and nerve conduction studies.

Conclusions

In conclusion, HIV-infected children may present with a wide array of primary neurologic manifestations resulting in considerable morbidity and mortality. Pediatricians should be aware of these varied presentations to improve the quality of care for HIV-infected children.

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