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It is now recognized that the virus that causes the acquired immunodeficiency syndrome (AIDS) attacks not only the immune system but also the nervous system. This virus, the human immunodeficiency virus (HIV), has been associated with several primary neurologic syndromes. Thus, AIDS has become a major neurologic disease as well. Approximately 10% of patients with AIDS present with neurologic symptoms, 40% or more eventually have major neurologic symptoms, and 80% have significant neuropathological findings at autopsy (1-3). Neurologic syndromes secondary to opportunistic infections and neoplasms associated with AIDS are well known (4).

The most common neurologic syndrome due to HIV is subacute encephalitis (1,5,6), which presents as a progressive dementia with prominent intellectual, behavioral, and motor abnormalities. The second most common "primary" neurologic manifestation of HIV is an unusual myelopathy (7,8), presenting with progressive paraparesis, sensory loss, spasticity, and incontinence. Aseptic meningitis, both acute and chronic, can be a manifestation of HIV infection (5). Less commonly reported neurologic syndromes associated with HIV include chronic distal symmetrical polyneuropathy, chronic polyradiculopathy, acute polyradiculopathy (Guillain-Barre syndrome), polymyositis, cerebral granulomatous angiitis (4,5,9-11), and movement disorders (12).

What is the evidence that HIV can infect brain tissue? The cells of the nervous system are infected as well as the lymphocytes, but which cells become infected and whether HIV is the causative agent responsible for neurologic symptoms are questions only recently addressed.

Synthesis of IgG antibody to HIV within the central nervous system (CNS) has been demonstrated in patients with AIDS and the AIDS-related complex (ARC) (13-15). Unique IgG oligoclonal bands were also present in the cerebrospinal fluid of AIDS and ARC patients with neurologic symptoms. The percentage of IgG against HIV in the cerebrospinal fluid is greater than that found in serum (13). Interestingly, such serologic findings have been found in patients who were neurologically normal (16).

Viruses may cause late effects on the CNS by several means: persistence in the CNS, autoimmunity, and secondary infection. Well-known examples of diseases with persistent CNS viruses include progressive multifocal leukoencephalopathy (papovavirus), kuru and Creutzfeldt-Jakob disease (infectious agents not yet fully identified), and subacute sclerosing panencephalitis (measles virus) (17). Such processes are well known in animals as well. Most pertinent to the HIV and its relationship to AIDS is the visna virus, which is a retrovirus like HIV and causes a slow, degenerative neurologic disease in sheep (18). Elevated cerebrospinal fluid production of IgG to the visna virus has been shown and interpreted as meaning primary CNS production of that antibody (18,19). HIV is more closely related taxonomically and genomically to the visna virus than to HTLV-I or HTLV-II (20). HIV has been placed, along with visna, with the slow virus (lentivirus) subgroup of viruses (21).

HIV has been directly cultured from cerebrospinal fluid and other neural tissue such as brain, spinal cord, and peripheral nerve (4,15,22). In one study, 24 of 33 AIDS and ARC patients with neurologic symptoms had HIV cultured from at least one neural tissue site, whereas none of 12 patients without neurologic symptoms had HIV cultured (15). This suggests that the neurological manifestations of AIDS are related to the presence of HIV in CNS tissue. Specifically, cells of the monocyte-macrophage line have been shown to culture HIV (23,24). The monocyte-macrophage cell may be the major cell in brain tissue that becomes infected with HIV (25,26).

HIV DNA sequences homologous to HIV RNA have been found in brain tissue of AIDS patients with neurologic disease. These sequences are contained in much greater amount in the brain than in the spleen, lymph node, liver, or lung (27). The DNA fragments are found in two forms: 1) integrated, suggesting tissue infection (28); and 2) unintegrated, representing the active replicating form of the virus (29). In situ hybridization studies, which examined brain tissue directly for viral specific DNA, have shown higher infectivity in brain than in most other tissue (27). Approximately 1% to 5% of brain cells are infected (23,27), and as much as eight times as many viral RNA copies per cell are found when compared to lymphoid cells. The in situ hybridization also has more definitively localized the HIV to the monocyte-macrophage cells, with lesser amounts to astrocytes and oligodendrocytes, and rarely to neurons (27). Identification of the neural cells is quite speculative and based only on the morphologic appearance of the cells. Lymphocytes were rarely seen. When they were seen, they did not pick up radioactive stain for viral RNA (27). In vitro, lymphocytes could not maintain virus production as well as macrophages. This is more evidence that macrophages are the primary cells involved in CNS infection with HIV (26).

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Case Reports

The following are cases from our institution illustrating some of the clinical and pathologic findings in patients with AIDS and neurologic disease.

Case 1

A 28-year-old black female with AIDS and *Pneumocystis carinii* pneumonia noted increasing fatigue and difficulty in caring for herself. During the past several months, others had noticed that she would not bathe, brush her teeth, dress completely, or clean her room at all. She was emotionally labile; she was sometimes loud and abusive and at other times would say very little.

Neuropsychological testing suggested moderate to severe deterioration from her estimated premorbid intelligence. She could not retrieve some basic facts, had difficulty with mental calculations, demonstrated a limited attention span, and could give similarities between nouns for only the most concrete items. Although globally alert and oriented to person, place, year, and month, she did not know the day of the month, her age, or her birthdate. Rote learning ability was moderately to severely impaired. In addition to psychomotor speed, mental flexibility and analytic skills were also impaired. She was coherent in conversation but produced errors in naming and repetition on formal testing. Marked physical and mental fatigue contributed substantially to her poor performance.

Over the subsequent eight months, her mental and physical condition gradually deteriorated. She was admitted to the hospital with diarrhea and *Pseudomonas aeruginosa* tracheobronchitis. She developed a thrombocytopenia of 28,000/μL. Despite vigorous supportive care, she became progressively lethargic and eventually died.

Gross inspection of the brain showed moderately narrowed gyri and widening of the sulci. Ammon's horn was markedly decreased in size bilaterally, with compensatory dilatation of the temporal poles of the lateral ventricles. Microscopically, perivascular lymphocytosis occurred in multiple areas, especially in the frontal and temporal regions. Reactive astrocytosis was prominent in the aforementioned areas and in the cerebellum. Loss of neurons was present in both dentate gyri. Both temporal horns had multiple glial nodules, satellitosis, and Alzheimer type II astrocytes. There was staining pallor in the pons, and loss of cells in the Purkinje and molecular layers of the cerebellum. The spinal cord showed vacuolization of the white matter bilaterally and in the posterolateral funniculi at all levels. The gray matter of the spinal cord showed some increase in number of astrocytes, but was otherwise unaffected.

Case 2

A 27-year-old white, homosexual male with AIDS and two months of diarrhea due to cryptosporidium began having difficulty with memory and concentration. He then began having visual and auditory hallucinations (seeing "strange" people and hearing accusatory voices) and became quite agitated. He improved on haloperidol, but showed further changes in his mental status.

His general physical examination was unremarkable except for moderate cachexia. On neurological examination, he was alert but oriented only to person and place. Emotionally, he was labile, at times being very agitated and then suddenly becoming calm and subdued. He showed a decreased attention span, impaired recent memory, and poor ability to concentrate. He had poor abstract reasoning and loss of goal-directed answers and questions. He showed concrete proverb interpretation. The rest of his neurologic examination was unremarkable. Computed tomography (CT) scan of the head was normal. EEG showed mild slowing, suggestive of a generalized cerebral disturbance.

The patient's psychotic features improved, but he continued to require close supervisory care by his family because of his cognitive deficits.

Case discussion

The first case illustrates some of the major neuropsychologic and pathologic findings seen in the AIDS dementia complex. The second case illustrates some psychiatric complications as well as the typical features of intellectual decline seen in patients with AIDS.

Subacute encephalitis, the most common of the primary neurologic syndromes due to HIV, presents as a progressive "subcortical" dementia or encephalopathy. "Subcortical" refers to diffuse cognitive deficits, psychomotor slowing, and early prominent motor abnormalities with a relative lack of "cortical" deficits such as aphasia or apraxia (1). The three basic clinical features are: 1) intellectual impairment, 2) behavioral changes, and 3) motor abnormalities. The term "AIDS dementia complex" has been coined to reflect these various features (1). These manifestations may present in any chronology or with any one feature predominating. The intellectual impairment usually begins as forgetfulness and loss of concentration. Patients complain of difficulty in remembering recent events, losing train of thought, and absentmindedness. These early cognitive abnormalities become progressively more apparent. Increasing slowness of thought, confusion, and disorientation follow. Neuropsychological testing initially may be normal or show only mild psychomotor delay (30). Inattention, distractability, difficulty with serial 7s, poor recall of objects, and impaired calculations, proverb interpretations, and abstract similarities can be present. Varying degrees of social inappropriateness occur, and a progressively impoverished speech eventually may lead to mutism.

Behavioral changes were slightly less common than dementia, but still a prominent finding in one-third of patients examined. Early manifestations include apathy and social withdrawal which progress to more severe neurovegetative signs, depression, and isolation. Patients with AIDS do have serious psychosocial problems, such as dealing with a fatal illness, guilt, and social isolation (2,31,32). Patients may develop more serious signs such as agitation, hallucinations, delusions, or other types of organic psychosis (31). Transient states of delirium may be seen as part of the underlying process or be precipitated by a deterioration in their medical condition.

Typically, no diminution occurs in level of consciousness. Even in the terminal stage of being bedridden and confused, they are "wide-eyed" and apparently alert.

Motor findings appear early and are a common manifestation of the AIDS dementia complex (1). Patients complain of increasing difficulty with walking, leg weakness, poor balance, and deteriorating handwriting. Ultimately, they may become bedridden with a spastic paraparesis or quadriparesis and incontinence (1). Frequently, patients have tremor, and myoclonus, seizures, or hemiparesis are present, though less common (1).

Head CT scan often shows generalized atrophy, but may be normal (33). The EEG may show diffuse nonspecific slowing (1,29,34,35). Cerebrospinal fluid is abnormal in 75% of cases, with either mild protein elevation, hypoglycorachia, or a mononuclear pleocytosis (5).

Children with HIV infection may show loss of previously attained developmental milestones and intellectual deterioration (35). Generalized weakness with pyramidal tract signs may progress to a spastic quadriparesis. Ataxia, dysphagia, and dysarthria have been noted. Seizures, myoclonus, and extrapyramidal rigidity are less commonly seen (36).

Head CT scans in children may show generalized cerebral atrophy, which in some cases was shown to have developed after a previously normal scan. Bilateral symmetrical calcifications of the basal ganglia

and periventricular white matter were seen in almost half of the cases studied (37). The calcium deposits were located in the walls of capillaries and larger blood vessels and may be a part of a vasculopathy caused by HIV (35,38).

Neuropathologic studies in the AIDS dementia complex have shown several nonspecific findings (2). The severity of the pathologic findings generally parallels the clinical symptoms, although this is not necessarily so in any one patient (39). White matter and subcortical gray matter are more severely affected than cortical gray matter (2). Pallor of myelin staining, astrocytosis of cerebral white matter, and fibrillary gliosis of cortical gray matter are the most common findings (2,3,40). These have been found in most, if not all, demented AIDS patients as well as in most of nondemented patients with AIDS. Whether these findings in the nondemented patients are nonspecific reactions or a harbinger of the subsequent development of dementia is unknown. These patients may also have subclinical dementia. The next most common white matter finding is vacuolation (2). This is most common in the internal capsule, brain stem, and cerebellum, and has been found in a higher percentage of demented patients, although there is much overlap with the nondemented patients (2).

Perivascular lymphocyte and macrophage infiltrates are found in the majority of patients, both the demented and nondemented (2,4). The lymphocyte and macrophage infiltration is often associated with foamy macrophages, both multinucleated and giant forms (2,3,41). These findings tend to be more common in the demented AIDS patients. Reactive astrocytosis seems to parallel the severity of the inflammation (2).

Microglial nodules are found in the brains of demented AIDS patients and consist of small aggregates of cells, primarily microglia and astrocytes. They are located predominantly in cortical and subcortical gray matter. Whether these nodules are primarily a reaction to HIV infection or coincident with cytomegalovirus infection is unknown (2,42). Other less common findings are coagulation necrosis, cavitation, vascular endothelial hyperplasia, perivascular calcification, and lipofuscin deposits.

Case 3

A 31-year-old white male, diagnosed with AIDS in March 1986, was admitted in November 1986 with increasing diarrhea. He had *Pneumocystis carinii* and cytomegalovirus pneumonia, oral candidiasis, and perianal herpes simplex. He began having syncopal episodes several months after the diagnosis of AIDS was made. Neurologic evaluation at that time revealed an intact mental status, with no evidence of memory loss, aphasia, agnosia, apraxia, or affective disorder. He did have evidence of a myelopathy, primarily manifested as pathologically brisk deep tendon reflexes in the lower extremities.

The patient's condition progressively deteriorated. The diarrhea worsened, and he developed respiratory distress and a waxing and waning level of alertness and cognition. CT scan of the head showed mild atrophy, and spinal fluid was unremarkable. He became progressively dyspneic and died on December 25, 1986.

Neuropathologic studies on gross examination showed a mildly dusky brain with a weight of 1400 g. Microscopically, there was a diffuse reactive astrocytosis with prominent glial nodules. Perivascular lymphocytosis and patchy perivascular demyelination was also seen. Focal areas of foamy macrophages were seen in the right amygdaloid nucleus. Slight vacuolization with macrophages was seen in the posterior columns of the thoracic cord.

Case discussion

The next most common primary neurologic manifestation of HIV is vacuolar degeneration of the spinal cord (7,15). Its presentation is similar to that of subacute combined degeneration of the spinal cord (vitamin B_{12} deficiency) with paraparesis, spasticity, ataxia, distal paresthesias, loss of vibratory and position sense, and incontinence. However, in patients with AIDS-associated myelopathy, progressive paraparesis and incontinence appear early, whereas sensory symptoms appear early and weakness and incontinence are later findings in subacute combined degeneration from vitamin B_{12} deficiency.

The pathologic findings in the myelopathy are those of a vacuolar degeneration. This is primarily located in the lateral and posterior columns (8) and is most severe in the thoracic region. The vacuoles are surrounded by a thin myelin rim, and occasionally are in continuity with the sheath of a myelinated axon. This implies that the vacuole was formed by swelling of the myelin sheath. The degree of the pathologic findings generally correlated with the severity of the clinical symptoms (2). These findings do resemble those seen in vitamin B_{12} deficiency (43); however, the patients studied had normal B_{12} levels, and all but one had normal folate levels (7).

Aseptic meningitis, both acute and chronic, can be a manifestation of HIV infection (5). Interestingly, it is more often found in the relatively immunocompetent host, ie, preceding the diagnosis of AIDS or ARC (5,44). It also has been seen in otherwise asymptomatic HIV carriers and as the initial manifestation of the acute infection with HIV. It presents with headache, fever, and meningeal signs. Cerebrospinal fluid is typical of an aseptic meningitis. If the meningitis becomes chronic or recurrent, there may be cranial nerve palsies or long tract signs (5). Pathologic findings are similar to those in subacute encephalitis (5).

Case 4

A 36-year-old black male presented in early 1985 with generalized lymphadenopathy, weight loss, and a positive HIV antibody titer. Over the following year he began complaining of painful dysesthesias in his upper extremities. There was no involvement of the lower extremities, and he denied motor weakness. He otherwise had no complaints, but a decline in his mental activity occurred, with increasing memory loss and changes in his personality. His physical examination was significant for generalized lymphadenopathy. Neurologic examination showed loss of pain sensation in the distal upper and lower extremities, primarily on the left. Nerve conduction studies showed decreased sensory nerve conduction velocity in both upper extremities. Motor nerve conduction velocities were normal, and amplitudes were not diminished. CT scan of the head showed generalized cerebral atrophy, and EEG was suggestive of a mild diffuse cerebral disturbance.

Case discussion

Several types of peripheral neuropathy have been described with HIV: a peripheral neuropathy with painful distal dysesthesias with moderate distal sensory loss, weakness, and atrophy, and absent or depressed deep tendon reflexes. Hyperactive reflexes may be present, suggesting CNS involvement (45). This is more often seen later in the course of infection with HIV, where the patient is more immunosuppressed. Dementia and/or myelopathy often accompany peripheral neuropathy, which then carries a poor prognosis (46). Electromyography and nerve conduction studies are consistent with axonal degeneration and segmental demyelination (47). This is to be distinguished from an inflammatory polyneuropathy described in patients with AIDS and ARC, which is much rarer (48,49). This type of peripheral neuropathy can be chronic or acute (Guillain-Barre syndrome) and is primarily demyelinating, with marked slowing of nerve conduction velocity. It is seen early in the course of HIV infection, often in asymptomatic carriers. Some patients are responsive to plasmapheresis or steroids, and prognosis is better than in the painful distal symmetrical polyneuropathy (46). Elevated cerebrospinal fluid IgG index (ratio of cerebrospinal fluid to serum IgG divided by cerebrospinal fluid to serum albumin) was uniformly present in five cases (5). Nerve biopsy showed chronic inflammation (four of five cases) or was normal (one of five cases) (5).

HIV has also been cultured from peripheral nerve tissue in patients with neuropathy and AIDS (15).

Conclusion

Numerous neurologic complications can accompany AIDS. Although much has been learned about AIDS, its virus, and its various manifestions, questions remain unanswered. Many manifestations are secondary to the immunologic deficiency, but several distinct syndromes which are not due to neoplasm, opportunistic infection, or debilitation have been described. Dementia, vacuolar myelopathy, peripheral neuropathy, and other syndromes have been found in association with the HIV particle itself and may indicate a possible relationship. Furthermore, HIV seems to have a propensity for neural tissue, specifically the monocyte-macrophage cell (4,50). How the monocyte-macrophage arrives at its destination (primarily subcortical white matter) is uncertain. Whether HIV is the sole cause of neurologic disease in AIDS remains unclear. Why some patients develop neurologic symptoms before any other manifestations of AIDS, whereas others are ravaged by the disease yet remain neurologically intact until death, is also unknown. Whether the CNS is tropic tissue analogous to lymphocytes or whether the relative lack of immunologic protection of the CNS is the fundamental basis for destruction by HIV is still another question that remains to be answered.

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