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Review Article

The Neurology of Paediatric AIDS

ACQUIRED immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV), is a multisystem disease that affects adults and children. Lesions in the disease may be due to the direct or indirect effect of the virus on the affected system. It has been established that the virus directly invades and destroys the lymphoreticular system, thereby ravaging the immunocompetence of the individual with all the adverse consequences. Apart from being lymphotropic, HIV is also neurotropic, and patients have been shown to harbour the virus in the brain and spinal cord.[1] In many such cases, the encephalopathy, or neurological symptoms, may predate the more typical symptoms of AIDS.[2] With fully established AIDS, central nervous system (CNS) dysfunctions have been documented in 60-90 percent of affected infants and children.[3] Histopathological examination of specimens obtained from patients with AIDS, have revealed lesions of inflammatory, degenerative, proliferative and neoplastic nature. The immunodeficiency associated with AIDS promotes disseminated infection from viral, fungal and bacterial agents in which the CNS is frequently involved. Neoplastic disorders such as malignant lymphoma occur with increased frequency in individuals infected with HIV, and involvement of the CNS is a common feature of AIDS-related lymphoma.[4] In adults, about 25 percent of AIDS-related lymphoma present as primary CNS disease and the brain may be involved along with other organs in 45 percent of cases.[4] Although seldom seen in children compared to adults, lymphoma of the brain has been identified as a component of the clinical case definition of AIDS. Other complications of undermined pathogenesis are vasculopathy and thrombocytopenia which may result in ischaemic necrosis and haemorrhage in the brain.

The impact of AIDS on the child can therefore, be due to multiple factors, any of which can operate singly or in concert. However, in the present communication, interest is focussed largely on the direct infection of the CNS of the child by the HIV. Brief mention will also be made of other associated and contributing aetiological factors.

Pathogenesis

In paediatric AIDS, the acquisition of the virus is most often through transplacental transmission from the mother. Postnatally, children may be infected through blood transfusion, penetrative sexual intercourse with HIV carriers and through injections with contaminated needles and syringes. Early evidence for the presence of the virus in the brain was provided by establishing HIV infection in chimpanzees who were inoculated with brain tissue obtained at necropsy from humans with AIDS.[5] The virus can be demonstrated in the brain by electron microscopy and *in situ* hybridization;[1] it has also been isolated from brain tissue and cerebrospinal fluid (CSF), by using reverse transcriptase activity in cell culture supernatants and confirmed by indirect immunofluorescence.[1] By *in situ* hybridization, the virus has been located in macrophages, microglia, giant cells and peripheral neurons.[6] It is thought that the invaded

mononuclear cells in the brain, release neurotoxic substances which cause injury to neural tissue.

Microscopic changes which have been related to HIV in the brain include gliosis, foci of necrosis, neuronal loss and demyelination, all involving minimal inflammatory changes.[7] There are characteristic multinucleated giant cells in the parenchyma and around capillaries. Other changes include vasculitis with vascular and parenchymal calcification which characteristically, involve the basal ganglia and frontal lobes;[3] microcephaly and cerebral atrophy are other common features of the syndrome. The spinal cord undergoes vacuolar degeneration and demyelination, particularly in the lateral and posterior columns.

Besides the primary CNS lesion of HIV infection, encephalitides related to opportunistic organisms such as *Cytomegalovirus, Herpes simplex,* varicella, *Papovavirus,* or meningitis and intracerebral abscess due to bacterial organisms and fungal agents such as *Cryptococcus neoformans* can occur in AIDS patients.[8] Very rarely, lesions of undetermined pathogenesis, such as thrombocytopenic intracranial haemorrhage and ischaemic necrosis related to arteriopathy, may compound the CNS pathology of children with AIDS.[8]

Clinical manifestations

The hallmark of HIV infection of the CNS in infants and children, is a progressive encephalopathy [9] characterised by developmental delay and impairment of cognitive ability associated with pyramidal and extrapyramidal tract signs. In congenital AIDS, latent period may exist before the development of the full clinical picture, months to years postnatally. Infants and young children under two years of age whose brain growth is very rapid, exhibit features of severe cerebral palsy such as diffuse spasticity, quadriparesis, athetosis and ataxia. Older children who had achieved appropriate milestones may present with mental deterioration, visual loss, sensory deficits, motor paralysis, speech disturbance and ataxia.[8] Other features of the disease at any age include seizures, microcephaly and signs of peripheral neuropathy such as paresthesia, muscle weakness and atrophy. In advanced cases, there can be multiple cranial nerve palsies with the fifth, seventh and eighth nerves most vulnerable.[2] In a recent review of seven children with AIDS in Calabar,[10] there were three cases with recurrent generalised tonic-clonic seizures; one of the patients had microcephaly, spastic quadriparesis and psychomotor retardation. The CNS problems of these three children could not be attributed to any other factors than to direct invasion of the brain by HIV.

Developmental delays are most pronounced in the areas of fine and gross motor skills and speech.[9 11] Specific deficits have been described in the areas of perceptual and visual motor skills, receptive and expressive language, as well as prelinguistic skills in younger children.[9] A serial neuropsychological testing commonly demonstrates a pattern of plateaus and deteriorations with an overall tendency towards a relentless downward progression in a majority.

Depressive symptomatology have been observed in children with AIDS.[11] This is manifested by apathy, social withdrawal and anorexia. Teenagers often develop a sense of low competence and low self-esteem in their educational experiences and social play. It is however, difficult to separate these depressive symptoms from those which can equally occur

in other chronic debilitating illnesses of childhood. Organic psychosis, manifested by manic symptoms, depression and paranoid tendencies along with other forms of personality alteration, have been observed in adults with AIDS.[2] Reports of similar psychopathology are lacking in children and adolescents. However, there is a report[9] involving a Haitian-American boy who had full-blown AIDS since the age of 9 years and subsequently presented with visual hallucinations, disorientation and depressive apathy when he was 12 years old. He had no prior history of psychiatric illness. Patients who present with both the neurological symptoms of HIV infection and other typical features of AIDS often deteriorate rapidly, resulting in a vegetative state and subsequent early death.

Diagnosis of HIV encephalopathy

This is based on the clinical symptoms coupled with the demonstration of HIV antigens or antibodies to the virus antigens in serum or CSF. However, when secondary opportunistic infections such as septic meningitis, cerebral abscess, or ischaemic necrosis due to vasculopathy are also present, it becomes difficult to separate the encephalopathic syndrome caused purely by HIV from that due to any of these other factors. The CSF usually demonstrates lymphocytic pleocytosis, increased protein and low glucose level.[12] Cranial CT and MRI scans may show ventricular dilatation and prominent cortical sulci, all indicative of cerebral atrophy, together with large areas of demyelination,[12] and calcification in the basal ganglia and frontal lobes. Electroencephalogram commonly shows diffuse bilateral slowing with epileptiform activities.[12]

Management

As at now, there is no effective treatment for HIV infection other than supportive measures. The resultant neural damage is not amenable to any of the currently available anti-HIV agents. However, CNS changes reflected by cognitive improvements, have been associated with zidovudine therapy.[11] This drug interferes with replication of the virus and therefore, functions within the sanctuary of the CNS to be effective.

Conclusion

Neurological dysfunction is an important component of the clinical spectrum of paediatric HIV infection. The retrovirus may directly damage the neural tissue causing progressive HIV encephalopathy, the manifestations of which may even forerun other well-known features of paediatric AIDS. It is therefore, pertinent that HIV infection should feature as a strong differential diagnosis in any infant who presents with unexplained neurodevelopmental delay or neurodegenerative disease. Since these processes are currently irreversible, ultimately incurable and therefore, potentially fatal, prevention becomes the central issue. Continuous efforts are necessary to identify and provide education and counselling to women and children at risk for HIV infection. The use of the anti-HIV drug, zidovudine, during pregnancy to prevent perinatal transmission, is presently under trial.

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