SUMMARY

INTRODUCTION
DIRECT HIV-I INFECTION OF CNS
INDIRECT HIV-I INFECTION OF CNS
OPPORTUNISTIC INFECTIONS OF CNS.

SUMMARY

HIV-I associated neurological diseases can manifest as an initial presenting clinical symptom in infants and children. Direct invasion of the CNS by the virus can be in utero or later in early life and can cause aseptic meningitis, encephalitis, HIV-I associated progressive encephalopathy with abnormal calcific vasculopathy and generalized brain atrophy and abnormal brain metabolism which can be demonstrated on CT, MRI and MRS scans of the brain respectively. The progressive encephalopathy causes impaired brain growth, delay or loss of developmental milestones and progressive motor dysfunction. Cerebrovascular complication can occur from direct viral invasion of cerebral vascular wall. The common non-directly related to HIV-I neurological disorders can be CNS lymphoma, opportunistic CNS infections, myelitis and rarely peripheral neuropathy, neuromuscular disorder and myopathy. Trial on AZT, protease inhibitor ritonavir therapies seems to ameliorate symptoms and return of normal neuroimage of progressive encephalopathy.

INTRODUCTION

Human immunodeficiency virus (HIV) can cause infection in children by vertical transmission (mother to infant) or by blood or blood products transfusion and rarely by child abuse. For those who were infected perinatally, they can be asymptomatic during the first few months of life. Approximately 10% of infected children die before 4 years of age; most of them succumb before 18 months of life whereas the majority of children survive beyond 5 years of age. Increasing numbers of survival infants and children show signs of CNS pathology which can be either primary or secondary to immunodeficiency. Up to 12% of perinatally infected infants (European Collaborative Study, 1990) and up to 18% of children and adolescents (Scott G et al, 1989; Janssen RS, 1992) show clinical features of progressive encephalopathy as a first sign of AIDS. Many neurological manifestations can be seen in pediatric AIDS which is quite different from adult HIV-I infection. The common neurological disorders are due to direct invasion of the central nervous system by HIV-I which can cause aseptic meningitis, subacute encephalitis, HIV-I associated progressive encephalopathy, vasculitis and cerebrovascular complication.

DIRECT HIV-I INFECTION OF CNS

Direct invasion of the CNS by HIV-I cause the most common neurological disorders in symptomatic children. The neurological abnormalities can be seen as early as the
first 2-3 months of life and can precede signs of immune deficiency and systemic illness or it can occur as late as 5 years of age (Burger JR, 1994). Recent evidence indicates early invasion of HIV-I to the brain in utero by the presence of HIV-I antigen in the brain tissues of stillbirth and abortive fetuses. (Grant I et al, 1987).

**Acute Meningitis.** In acute meningitis caused by HIV-I, the pictures will be like aseptic meningitis with other viruses i.e. fever, headache, stiff neck and back with retained consciousness. Some cranial nerves paralysis can occur. The CSF shows mild lymphocytosis with normal glucose and slight increase in protein content. HIV-I can be cultured from the CSF. At present no definite treatment can cure this disease.

**HIV-I Associated Progressive Encephalopathy.** This disorder is more common than meningitis and can be found in 30-50% of HIV-I infected infants and children (Ebstein LG et al, 1988). Presence of HIV-I antigens (p 24, p 41) and HIV DNA in the brain and CSF and virus-laden macrophages and multinucleated giant cells in the autopsied brain, especially of the glial cells which are CD4+ lymphocytes receptors, support direct invasion of the CNS by this virus.

**Pathophysiology:**

Pathologic changes in brain can be from 3 mechanisms.

1. **Direct invasion of HIV-I virus to brain cell by hematogenous circulating infected T lymphocytes and macrophages.** The HIV-I virus will affect CD4 lymphocytes receptor (cerebral astrocyte) resulting in production of toxic substance damaging neurons and blood brain barrier.

2. **By immunomediated mean, the virus itself will stimulate the macrophages and infected neurons to produce toxic substance inducing inflammation and destruction of myelin and nerve cells.** These toxic substances can be cytokines, chemokines, tumor necrosis factors alpha, platelet activating factors. The viral enveloping glycoprotein (gp 120) antigen can also stimulate the macrophages to release substance which can block the function of neuronal enzyme receptor (N-methyl-D-aspartate, NMDA) result in failure of prevention of toxic substance produced by virus and infected glial cells to damage neurons.

3. **Toxic substance produced by HIV-I virus and infected glial cell will cause unwanted oxidative stress leading to neuronal death (apoptosis).**

**Pathology:**

The infected brain revealed patchy or diffuse demyelination in the deep white matter and sometimes gray matter of cerebrum and cerebellum with scattered multinucleated giant cells (MGC) and little inflammatory reaction (progressive diffuse leukoencephalopathy). The pathohistological pictures can also be multinucleated giant cells encephalitis, characterized by accumulation of MGC and macrophage laden with viral HIV-I particles, prominent inflammatory reaction and focal necrosis with loss of neuronal cells. Calcific deposits of mainly small sized cerebral vessels, especially of the basal ganglia and the deep hemispheric white and gray matters can occur and cause typical picture of butterfly lesions from calcified basal ganglia in the CT or MRI scans of the brain which is documented to be pathognomonic signs of HIV-I associated progressive encephalopathy (Kleihues P et al, 1991).

**Clinical manifestation.** The clinical manifestations of HIV-I associated encephalopathy in small children can be global delay, static or regression of development and can result in acquired microcephaly. Progressive spastic paralysis of all limbs with positive pyramidal tract signs, signs of basal ganglia dysfunction, ataxia, myoclonic jerk and frank seizures can be seen in the process of progressive encephalopathy. Seizures are frequently encountered about 18% in pediatric AIDS and are mainly due to febrile
convulsion or in association with opportunistic infections of the CNS (Gray F et al, 1988). The CSF in the HIV-I encephalopathy is usually normal but may show mild lymphocytosis with normal sugar and mildly increased protein content. HIV-I virus can be cultured and HIV-I viral particles can be demonstrated from the CSF by PCR method. For the older children, impaired cognitive function, slow progress or regression of learning, impaired expressive conversation, comprehension, perceptual motor activity and also attentional difficulties are main symptoms.

Radiological imaging study. Decarli C. et al in 1993 studied 100 consecutive CT scans of the brain of symptomatic children with HIV-I infection who may have encephalopathy. They found generalized cortical atrophy, ventricular enlargement, white matter attenuation (leukoaraiosis) or cerebral calcification in 86% of the patients studied (Fig. 1). Cerebellar atrophy appeared in 12% of the children. Only 65% of the children were encephalopathic at the time of evaluation. All 16 children with cerebral calcification (of basal ganglia) had the signs of encephalopathy at the time of the study and all had HIV-I infection through vertical transmission. CT measures proved to have a specificity and a sensitivity of only 76 percent. The CT abnormalities, if seen in children without encephalopathy can suggest presymptomatic brain disease in these children. The presence of cerebral calcification on CT scan brain suggest HIV-I infection in utero with encephalopathy. Galgani S, et al. in 1990 reported findings in MRI and SPECT scans in the children with different stages of HIV encephalopathy. MRI scans were positive in 80% of patients and showed cerebral atrophy (mild, moderate, severe) and white matter lesions which can be punctate, patchy or diffuse attenuation. SPECT abnormalities can be distinguished in focal, multiple and diffuse uptake defects and found to be abnormal in 94% of patients. All kinds of lesion can be detected at stage II-IV of encephalopathy (according to Price, 0-4 stages). SPECT scan was also found to be a very sensitive technique, showing uptake defects in a high percentage of asymptomatic HIV infected patients.

Fig. 1 CT scan brain: generalized cortical atrophy with ventricular enlargement and calcified basal ganglia (arrow). (Ref. D. Carli C et al, Ann Neurol 34(2): 198-205, 1993.)

Fig. 2 MRA: Fusiform aneurysmal dilatation of suprachinoid portion of Rt. ICA extending to all segments of ACA and MCA. Blood clot or thrombosed aneurysm arising from suprachinoid Rt. ICA projecting posteromedially and suggesting site of bleeding. ICA = Int. carotid artery.
ACA = Anterior cerebral artery.
MCA = Middle cerebral artery.
(Ref. Shah SS et al, AJNR 17: 1913-17, 1996.)
Magnetic resonance spectroscopy (MRS) and imaging (MRI) were studied in 63 HIV adult patients (16 asymptomatic, 47 had AIDS dementia complex) by Vion-Dury J et al in 1994. The findings in MRS showed significant modifications of brain metabolism and the most sensitive metabolic parameter is the N-acetyl-aspartate/choline ratio. The correlation between MRS and MRI is good in 75% of patients. In 4 of 16 neuroasymptomatic patients (25%), a metabolic encephalopathy were found while MRI were still normal. Two patterns of abnormal brain metabolism were seen corresponding to HIV encephalitis and HIV-related progressive leukoencephalopathy. At present no data on children was available.

Trial on antiviral therapy:

Zidovudine (AZT) therapy

Pizzo PA et al in 1988 reported some improvement in neurodevelopmental abnormalities in 13 children who had presented with encephalopathy before treatment with I.V. infusion of Zidovudine (AZT). Serial measurements of IQ before therapy and after 3 and 6 months of continuous therapy with AZT (0,9-1.4 mg per kilogram per hour) showed that IQ scores including those for verbal and performance IQ, rose in these 13 patients and also in 5 other children who had no detectable clinical evidence of encephalopathy before treatment. The improvement in appetite and weight, decreased lymphadenopathy and hepatosplenomegaly, decreased immunoglobulin levels and increased number of CD4 cells can also be seen. In some patients the improvement in the features of encephalopathy occurred despite the absence of immunologic improvement. Tozzi V et al (1990) also showed that oral zidovudine of at least 500 mg per day can cause improvement of neurological dysfunction in patients with HIV encephalopathy and reversal of MRI and SPECT abnormalities in some patients. The improvement was often seen within few weeks of treatment and in most cases were maintained up to 12 months. Galgani S, at al in 1991 reported that HIV encephalopathy in adult AIDS which was associated to myelopathy, but not myelopathy itself, improved significantly with AZT therapy.


Dideoxyinosine, dideoxy cytidine therapy

Balis FM et al (1992) gave dideoxyinosine (ddI) and dideoxycytidine to the patients with HIV-encephalopathy and reported definite return of abnormal MRI head scans to normal or nearly normal scan.

Protease Inhibitor (PI) therapy

Danner SA et al (1995), Markowitz M et al (1995) reported good responses of using protease inhibitor e.g. Ritonavir (RTV) in adult AIDS. They found significant decreasing number of viral load and increased number of CD4. Cameron DW et al (1996) reported prolonged life in the final state of AIDS patient who received Ritonavir. Mueller BU et al (1996) gave Ritonavir to children with HIV-I infection. He found that all children could tolerate the RTV drug quite well and were able to destroy the HIV viruses.

Tepper VJ et al (1998) reported marked improvement in intelligence, especially speaking and writing, reduction of number of viral load and increased number of CD4 with return to normal of previously abnormal MRI head scan in an 8 years and 2 months old child who received combination treatment of RTV, ZDV and 3TC for 6 months.
He believed that the improvement caused by reducing number of viral load and resulting in decreased toxic substance produced by the virus and infected glia cells affecting the neurons.

**Cerebrovascular complication.** As the result of direct invasion of HIV-I to the endothelial wall of blood vessels which is mainly large or medium sized arteries, the affected arteries showed marked intimal fibroplasia with marked thickening of the wall, macrophages laden with viral particles with rare multinucleated giant cells and some destruction of elastica lamina. The arterial sclerosis of the large and medium sized vessels results in fusiform aneurysmal dilation of mainly the major vessels of the circles of Willis (Fig.2) and some of large leptomeningeal arteries of the temporal lobe and cause non-hemorrhagic or hemorrhagic infarctions from vascular occlusion. (Dickson DW et al, 1984) Sudden fatal cerebral hemorrhage due to rupture of the aneurysm can occur. (Park YD et al, 1990, Shah SS et al, 1996). The incidence of the cerebral hemorrhage in pediatric AIDS is around 13 percent (Kozlowski PB et al) which is quite closed to 1.6-12% found in adult AIDS patients (McArthur JC 1987).

**INDIRECT HIV-I INFECTION OF CNS**

The neurologic symptoms not related to direct invasion of HIV-I can be from the opportunistic infections which are acquired easily in AIDS children due to immunodeficiency. The most common infection reported in European literatures is CMV infection while bacterial, tuberculous and fungal infections are quite common in children with AIDS in Thailand and Asian countries. When comparing with adult AIDS, toxoplasmosis and JC virus infection are rarely found in the children infected with HIV-I. Primary lymphoma was reported to be the most common cause for intracranial mass lesion in children with AIDS (Ebstein LG et al, 1988). No report of primary lymphoma or other intracranial tumors is found from Asian countries. Vacuolar myelopathy was seen in the spinal cord of adult AIDS while myelitis is more common in pediatric AIDS (Dickson DW et al, 1984). Myelinopathy and axonopathy are also reported due to degeneration of corticospinal tract. Peripheral neuropathy and neuromuscular disorder are mainly found in adult AIDS but are rarely reported as neurological complication in pediatric AIDS. Sensori motor axonal neuropathy and demyelinating neuropathy can be seen in older children. (Floeter MK et al, 1997). Proximal myopathy with myalgia and increased muscle enzymes are rarely reported in adult patients and has never been reported in children and are due to HIV-associated polymyositis or Zidovudine-associated myopathy.

**OPPORTUNISTIC INFECTIONS OF CNS**

The opportunistic infections occurred easily due to the underlying immunodeficiency in the pediatric patients. Cytomegalovirus (CMV) and Candida albicans were reported as common pathogens in Europe and America, while pyogenic and tuberculous meningitis and cryptococcal meningitis were very common in HIV-I infected children in Thailand and Asian countries. Cerebral toxoplasmosis and JC virus causing progressive multifocal leukoencephalopathy (PML) was rarely seen in children. In adult the common opportunistic infections are quite different from children and are from cryptococcus, toxoplasma, cytomegalovirus and JC virus. Another common virus causing acute meningitis and encephalitis in infected children is herpes simplex virus (Poneprasert B et al, 1995). Severe pyogenic or tuberculous meningitis or cryptococcal meningitis with severe sepsis (of the same organism) can be the first manifestation of severe immunodeficiency in the HIV-I infected children.
The clinical manifestations are dependent on the causative organisms of the CNS infections. In pyogenic meningitis, the child will have acute fever, headache, vomiting, tense fontanel in small child, stiffneck in older child, with typical changes of CSF in bacterial meningitis. Children with prolonged fever, headache, vomiting, convulsion, and stiff neck with or without change of consciousness should alert the physician of chronic meningitis with Mycobacterium tuberculosis or fungus (C. neoformans, Penicillium manefi). Lymphocytosis with increased protein and decreased sugar content can be seen as a typical changes in tuberculous or fungal meningitis while increased polymorphonuclear cells is seen in purulent meningitis. The patients can have repeated attacks of severe pyogenic meningitis due to the presence of immunodeficiency status. The definite diagnosis of CNS infections can be obtained from good history taking, physical examination, CSF examination and culture, specific serology, detection of antigen for Mycobacterium and fungus in CSF and also typical radiological change in the CT or MRI scan of the brain. The treatment will depend on the type of causative agents i.e. antibiotics for pyogenic meningitis, antituberculous drugs for tuberculous meningitis and amphotericin B with or without flucytosine for the cryptococcal meningitis. Cerebral toxoplasmosis responds quite well to pyrimethamine with folinic acid and sulfadiazine or trisulfapyrimidine or clindamycin. Intravenous acyclovir can be used in CNS infection with herpes simplex and chickenpox viruses while ganciclovir is an effective treatment for cerebral CMV infection or CMV retinitis. Oral Itraconazole or fluconazole is use as suppressive therapy for cryptococcal meningitis while combination of oral pyrimethamine with folinic acid and sulfadiazine are used as suppressive treatment for cerebral toxoplasmosis for the whole life. The patients who suffered from these opportunistic infections, if treated early can recovered from the diseases. The children who have associated severe septicemia or bacteremia can rapidly lead to death or have severe neurological sequelae if they survived.

References