A young man with organic psychosis

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A 24-yr old gentleman was referred for evaluation for organic causes of psychosis. He had presented with altered behaviour for the last 3 months. He had progressive decline in cognitive functions as evidenced by inability to cope with work, inability to concentrate and difficulty in reading. He had a failing memory. He had history suggestive of behavioural abnormality as evidenced by lack of self-care, hallucinatory behaviour and abusive language since the last 3 months. He had hallucinations and delusional beliefs but no symptoms to suggest confusion. Since the last 1 month he had become partially dependent on his parents for activities of daily living. He also gave a history suggestive of motor weakness - since 6 weeks prior to admission he had noticed unsteadiness of gait with a tendency to sway to the right. He had no history of bladder or bowel incontinence.

He gives no past history of psychiatric illness, significant stressful life events or intravenous drug abuse.

He had no fever or diarrhoea preceding the onset or during the illness. However his parents noticed that he had significant loss of weight and appetite. He had never received blood transfusion but admitted to having contact with commercial sex workers.

General examination revealed pallor with no lymphadenopathy, oral candidiasis or Kaiser-Fleiser ring. CNS examination revealed features of frontal, temporal and parietal lobe dysfunctions. The mini-mental state examination done revealed a score of 20 on 30 with evidence of impaired attention, judgement, and memory. Fundus examination was normal. He had no cranial nerve dysfunction. Motor system examination revealed hyperreflexia with equivocal plantar reflex bilaterally. He had bilateral cerebellar signs (right more than the left). He had no evidence of a peripheral neuropathy. Other systemic examination was normal.

At this point what is the possible differential diagnosis?

Given the risk for HIV infection the possible differential diagnoses include all CNS infections, Wernicke’s encephalopathy, CNS lymphoma, Hydrocephalus, toxic and metabolic encephalopathies.

The investigations done at this time revealed mild anaemia - Haemoglobin: 7.5g%, with an MCV of 70 and Blood Picture showing a microcytic hypochromic picture. The Total WBC Count was 3000/cu mm and the differential WBC Count revealed neutrophils 58, eosinophils 7, lymphocytes 28, Monocytes 3, Band forms 4 and the Absolute lymphocyte count was 840. His Bone marrow examination was non-diagnostic.

CSF: Total WBC count showed 25cells/cu mm with a differential count of Neutrophils 86 % and lymphocytes 14 %. CSF chemistry revealed Sugar: 59mg% with a concomitant plasma glucose: 156mg%; Protein: 42mg%. The CSF was negative for cryptococcal antigen by India ink and culture. The gram stain and culture were negative.

Blood and CSF VDRL was negative. Thyroid function tests were normal. CT Brain: revealed Diffuse Cerebral atrophy, Ventricular enlargement and Cerebellar atrophy. His HIV ELISA was positive.

Why should we do a CSF examination in this patient?
The possible differential diagnosis mostly related to infections of the CNS. Pyogenic, tuberculous and cryptococcal meningitis can be easily diagnosed by CSF examination. The CSF VDRL helps in the diagnosis of Neurosyphilis.

This young man with HIV infection, who presented with organic psychosis, had features also of decline in cognitive functions, motor skills and behavioural abnormalities. These clinical features suggest that the patient’s psychosis is organic rather than functional. Brain imaging showed diffuse cortical and cerebellar atrophy. CSF examination was non-contributory. HIV serology was positive. In view of the above features and in the absence of other organic cause for the same, a diagnosis of AIDS dementia complex (ADC) or HIV encephalopathy was made.

ADC is the initial AIDS defining illness in up to a maximum of 3% of people infected with HIV. About one-fourth of the patients with AIDS, develop ADC sometime in the course of the illness. This is usually seen with severe HIV-1 infection associated with severe immunosuppression. ADC when severe is associated with limited survival. ADC as the initial presentation especially in a young patient
who otherwise does not have any of the AIDS-defining illnesses is so far not documented in India. With the prevalence of AIDS steadily increasing ADC may become a far more common presentation.

What CNS infections can mimic AIDS dementia complex?
1. Some patients with primary CNS lymphoma located deep in the frontal white matter near the lateral ventricles especially when bilateral present similarly.
2. Hydrocephalus can also present similarly.
3. CMV encephalitis is one of the diagnostically more difficult conditions to distinguish from ADC. Intractable seizures, cranial nerve deficits, hyponatremia are common associates of CMV encephalitis. In a recent study that looked at the aetiology of new onset seizures in HIV patients, ADC was identified as the cause of the seizures in only one of the 23 patients (4.34%).
4. In contrast toxic and metabolic encephalopathies usually leads to a reduced level of arousal.

What other tests are useful in ruling in or ruling out the diagnosis of ADC?
The most useful tests in this setting include Vitamin B12 assay, CSF analysis, neuroimaging, and formal neuropsychological testing.

CSF examination rules out the other differentials; there may be mild elevation in proteins, and mild mononuclear pleocytosis. CSF viral load and p-24 though positive is not sufficiently specific for ADC and hence not necessary. Elevated levels of b2 microglobulin and neopterin are also present.

Neuroimaging is necessary to detect evidence such as mass lesion of primary CNS lymphoma or ependymal signal changes of CMV encephalitis. Evidence of cerebral atrophy with widened cortical sulci and enlarged ventricles are usually noted in patients with ADC especially stage-II onwards. Additionally MRI in some patients detects T2 weighted patchy or fluffy signal abnormalities in the hemispheric white matter, basal ganglia, or thalamus and evidence of white matter pallor.

Once the diagnosis of ADC is made, a five step ADC staging system is applied. The designation is based on degree of functional incapacity in cognitive and motor activities of work and daily living. The ADC staging system is as given below.

In the multicentered AIDS cohort study (MACS), which followed a selected group of gay men, the incidence rates of ADC over a five-year period were shown to increase with a corresponding decrease in the CD4 cell count. The incidence per 100 person years of ADC in patients with CD4 counts <100 was 7.43;CD4 between 101 to 200 was 3.04; CD4 between 201 to 500 was 1.31 and for those with a CD4 cell count more than 500 the incidence per hundred patient years was only 0.46. This data suggest that severe immunosuppression has a strong permissive effect on the development of ADC, but alone is neither sufficient nor absolutely necessary for ADC to manifest.

What is the pathology seen in the Brain?
The pathology seen in the brain shows evidence of microglial nodules, multinucleated giant cells, abortive infection of astrocytes, absence of infection of neurons and oligodendrocytes, white matter pallor, reactive astroctysis, perivascular mononuclear cell infiltrates, dendritic simplification and neuronal loss.

What is the pathogenesis of AIDS dementia complex?
Human immunodeficiency virus (HIV) infection of the nervous system is unique when compared with other viral encephalitides. Neuronal cell loss occurs in the absence of neuronal infection. Viral proteins, termed “virotoxins,” are released from the infected glial cells that initiate a cascade of positive feedback loops by activating uninfected microglial cells and astrocytes. These activated cells release a variety of toxic substances that result in neuronal dysfunction and cell loss. The virotoxins act by a hit and run phenomenon. Thus, a transient exposure to the proteins initiates the neurotoxic cascade. High concentrations of these proteins likely occur in tight extracellular spaces where they may cause direct neurotoxicity as well.

What is the treatment for ADC?
Though there are no specific regimens for ADC, the current consensus includes:
1. ADC patients should be treated aggressively with HAART
2. Combinations of 3 or more drugs should usually be used.

This should preferably include at least two drugs with appreciable penetration of blood brain barrier. Among the NRTIs, Abacavir, Zidovudine, and Stavudine; among the NNRTIs, nevirapine and among the PIs, indinavir penetrate the blood brain barrier appreciably.

HAART therapy results in rapid improvement in cognitive function.
Improvement in neuropsychiatric test scores has also been seen.\(^1\)

The patient was evaluated and the benefit of Highly active antiretroviral therapy (HAART) was explained to him. He was advised a combination of antiretroviral drugs including Zidovudine, Nevirapine and Indinavir. However due to cost constraints he could not start the medication immediately and started the medication after going back to his hometown. We are planning to follow him at regular visits and along with routine history and examination do formal neuropsychological evaluation including the Minimental state evaluation at every visit.

**What are the other drugs, which have shown benefit in ADC?**

Recent studies have also shown benefit in terms of Selegeline a monoamine oxidase B inhibitor and putative anti-apoptotic agent in terms of definite improvement in verbal memory and cognitive function in patients with ADC.\(^9\)

**Are there any cautions in the treatment of ADC?**

Neuroleptics should be used cautiously as there is an increased risk of extrapyramidal side effects in these patients. Rarely, paradoxically, antiretrovirals can cause psychosis. However this develops after starting therapy, responds well to cessation of the antiretrovirals and to low dose antipsychotics.\(^10\)

**References**