

26. HIV-1 associated Encephalopathy and Myelopathy

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HIV encephalopathy

The primary cause of HIV encephalopathy (HIVE) is the infection of the CNS caused by HIV. If untreated, some 15-20 % of patients will eventually develop the disease. Since the introduction of highly active antiretroviral therapy (HAART) the incidence of the disorder has decreased. Other terms used for this condition with largely the same significance are AIDS dementia complex, AIDS dementia, HIV dementia, and HIV associated cognitive motor complex. HIVE only occurs in the later stages of the HIV infection when there is a profound immune suppression (CD4+ T-cells < 200/ μ l). The incidence of HIVE will likely increase in the developed countries as a consequence of increasing life expectancy (Valcour 2004).

In HIVE there is a high level of replication of HIV in macrophages and microglial cells of the brain. Neuronal cells have not consistently been shown to be infected. However, different immunopathological mechanisms lead to functional and structural damage of these cells. With respect to viral replication and viral quasispecies the CNS is partially independent from the hematolymphatic compartment (Eggers 2003). In HIVE the viral load in the brain parenchyma and the cerebrospinal fluid have been shown to be high, and to loosely correlate with the extent of the disease.

Clinical manifestation

HIVE is considered to be a subcortical dementia. HIVE emerges over the course of weeks and months. Acutely developing symptoms point out to another etiology. Fever, exhaustion, the effects of tranquilizers and reduced physical condition, e.g. with opportunistic infection, may all mimic dementia. In these cases, diagnosis of HIVE can only be made after repeated examinations when the condition mimicking dementia has improved.

Symptoms are occasionally noted earlier by relatives than by the patient himself. This is why a history given by these persons is of utmost importance. Typical complaints are slowing of reasoning, forgetfulness, difficulties concentrating, lack of energy drive, mild depressive symptoms and emotional blunting. For symptoms and signs see Tables 1 and 2.

Impairment of alertness, neck stiffness and focal or lateralising neurological signs (e.g. hemiparesis, aphasia) are not typical for HIVE. Psychotic symptoms without cognitive or motor disturbance do not warrant a diagnosis of HIVE. The coincidence of psychosis with HIVE is rare. Focal and generalized epileptic seizures are rare manifestations of HIVE.

The severity of HIVE may functionally be categorized according to the Memorial Sloan Kettering scale (Table 3) (Price 1988).

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Table 1: Symptoms of HIVE including history given by close relatives or companions	
Cognition	Forgetfulness, difficulties concentrating, mental slowing (apprehension, processing)
Emotional	Loss of drive and initiative, withdrawal from social activities, failure to manage the financial and administrative aspects of one's life. Depressive mood, emotional blunting
Motor	Slowing and impairment of fine movements (e.g. typing, buttoning up), and disturbance of gait
Autonomous	Impaired micturition (urgency), loss of sexual libido, erectile dysfunction

Table 2: Signs with HIVE	
Neurological findings	<p>Early stages: impaired gait, slowing of rapidly alternating movements, hypomimia, occasionally tremor and short stepped gait</p> <p>Later: brisk tendon reflexes, positive Babinski sign, slowing of gaze saccades, sphincter impairment including incontinence. Palmomental, grasp and glabella reflexes. Occasionally accompanying polyneuropathy</p> <p>In the terminal stages spastic tetraplegia and dual incontinence</p>
Neuropsychological findings	Slowing of psychomotor speed (e.g. naming the months in reverse), impairment of short term memory (recall of verbally presented items, digit span), and mental flexibility (spelling simple words backwards)
Psychological findings	<p>Early stages: emotional blunting, disappearance of strong personality traits, distractability, loss of initiative</p> <p>Later: problems with recalling events in the correct time order, disorientation to time, space and situation. Finally mutism</p>

Table 3: Severity of HIVE	
Stage 0:	(normal) normal mental and motor function.
Stage 0,5:	(equivocal/subclinical) no impairment of work or capacity to perform activities of daily living (ADL); normal gait; slowing of ocular movements and movements of extremities may be present
Stage 1:	(mild) able to perform all but the more demanding aspects of work or ADL, but with unequivocal signs or symptoms of functional, intellectual or motor impairment; can walk without assistance
Stage 2:	(moderate) able to perform basic activities of self-care, but cannot work or maintain the more demanding aspects of daily life; able to walk, but may require a single prop
Stage 3:	(severe) major intellectual incapacity (cannot follow news or personal events, cannot sustain complex conversation, considerable psychomotor slowing); motor disability (cannot walk without assistance, usually manual slowing and clumsiness)
Stage 4:	(end stage) almost mutistic. Intellectual and social comprehension and output are at a rudimentary level; almost or completely mute; paraparetic or paraplegic with urinary and fecal incontinence

Diagnostic workup

Making an HIVE diagnosis requires a synopsis of clinical information and the results of laboratory tests. No laboratory test result on its own warrants the diagnosis of HIVE. Rather, the diagnosis requires the exclusion of other conditions (Table 3).

Clinically, the cognitive and psychological signs and symptoms are invariably accompanied by motor signs, although these may be subtle (Table 2). The International HIV dementia scale (Sacktor 2005) is an easy-to-use bedside instrument for the detection and quantification of the cognitive impairment of HIVE.

Laboratory tests are mainly employed to exclude differential diagnoses. MRI should be preferred to CT. MRI often shows patchy, diffuse, hyperintense and relatively symmetrical lesions in the white matter. These changes indicate leukoencephalopathy. In addition, atrophy with enlargement of the ventricles and the extra-ventricular CSF spaces may be seen. However, none of these findings are specific for HIVE, and the disease may be present with a normal MRI. Unlike in PML the white matter lesions do not affect the cortical U-fibers, i.e. they don't reach the cortical ribbon. Edema and space occupying lesions are not typical for HIVE and should raise suspicion of other conditions. There may be some faint contrast enhancement symmetrically in the basal ganglia.

CSF analysis shows a normal to even decreased white cell count. In contrast, total protein and albumin concentrations may be slightly elevated (blood-brain-barrier disruption). Oligoclonal bands and increased IgG-index indicate autochthonous immunoglobulin production within the CNS. However, these findings are unspecific and are frequently present in the asymptomatic stages of HIV infection. Although there is a statistically significant correlation of a higher CSF viral load with HIVE, this association is of little value in the context of an individual patient. The EEG shows no or only mild signs of generalized slowing. Moderate or severe slowing or focal arrhythmic delta activity are atypical for HIVE.

Treatment

According to the pathogenesis of HIVE, treatment should aim at suppressing the viral replication in the CNS. It is an unresolved issue whether the antiviral compounds need to penetrate into the CSF. A variety of clinical (Letendre 2004), virological (de Luca 2002), pathological and electrophysiological studies suggest that substances reaching higher CSF concentrations are more effective. In contrast, we found no association of the number of CNS-penetrating substances and their CSF levels with the magnitude of CSF viral load suppression (Eggers 2003). HAART-induced neurocognitive improvement correlates more closely with viral load suppression in the CSF than in the plasma (Marra 2003).

In the absence of prospective, controlled, and randomized studies with clinical end points, we consider it important that any antiretroviral regimen in patients with HIVE includes as many as possible CNS-penetrating substances. We suggest any of the following: zidovudine, lamivudine (high concentrations in *ventricular* CSF; unpublished observations), nevirapine and indinavir. With the substances approved for clinical use in the recent years, CNS penetration is low or unknown.

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Table 4: Differential diagnoses of HIV encephalopathy and diagnostic workup

Condition	adequate diagnostic step (commentary)
Neurosyphilis	Antibody testing and CSF analysis (pleocytosis >15/ μ l) (serological findings may be atypical for active neurosyphilis)
CMV encephalitis	CSF (pleocytosis, potentially granulocytic; decreased glucose elevated total protein) PCR for CMV in CSF, CMV antigen (pp65) in blood antibody testing in blood and CSF (IgG and antibody index may be increased) MRI (potentially subependymal hyperintensity and contrast enhancement) Occurs mostly in association with manifestation of other organs (retinitis, colitis, pneumonitis, esophagitis)
Toxoplasmosis	CT / MRI (single or multiple lesions found most frequently in basal ganglia or thalamus, space occupying effect, edema, frequently with contrast enhancement (patchy or ring-shaped)) Presence of toxoplasma specific IgG in blood and CSF (rarely total seronegativity) (may rarely pass as diffuse microglial nodule encephalitis)
Primary CNS lymphoma	CT / MRI (single or multiple lesions most frequently adjacent to ventricles, space occupying effect, edema, almost invariably intense contrast enhancement (patchy more than ring-shaped)) CSF cytology EBV PCR in CSF (HIV-associated CNS lymphomas EBV induced) PET or SPECT (tracer enhancement in lesion)
VZV encephalitis	CSF (marked inflammatory signs) VZV specific IgG in blood and CSF (IgM may be absent) VZV PCR in CSF Mostly antecedent or accompanying cutaneous zoster lesions
Cryptococcal meningitis	CSF (opening pressure frequently elevated, cell count and protein may be normal), India ink stain Cryptococcal antigen in blood and CSF, fungal culture
Tuberculous meningitis and other bacterial infections	CSF, culture, PCR for mycobacteria appropriate tests
Progressive multifocal leukoencephalopathy (PML)	MRI (single or multiple lesions of white matter, no space occupying effect, no edema, no contrast enhancement) PCR for JC virus in CSF
Intoxication	Determination of drug levels / screening for illicit drugs
Metabolic encephalopathy and impaired general physical condition	Determination of electrolytes, renal and hepatic markers, hormones (thyroid, cortisol), blood count Hypoxaemia? (blood gas analysis) Reduced physical state? (bed ridden, wasting, pyrexia)
Depression with „pseudo dementia“	Psychiatric examination
Other „subcortical“ dementia forms	Normal pressure hydrocephalus, Parkinsonian syndroms, other neurodegenerative conditions, subcortical arteriosclerotic encephalopathy

A number of small studies investigated the effect of Selegelin, Nimodipin, Lexipafant, and valproic acid for treatment of HIVE. These drugs act on the molecular pathogenesis of HIVE and are used in conjunction with antiretroviral treatment. Although a trend for clinical and neuropsychologic improvement was seen with some substances, none of them can be recommended for clinical routine.

Prognosis: An optimal HAART may lead to significant clinical improvement of HIVE. The extent of improvement includes restoration of working ability in patients previously dependent on caregivers. This effect can be observed for up to four years, in parallel with sufficiently suppressed plasma viraemia (Cysique 2006). During the first months of treatment, the radiological signs of leukoencephalopathy may become more prominent, but eventually regress over the following one to two years.

Autopsy studies and clinical case series show, however, that some patients develop a clinically apparent CNS disease despite effective HAART-induced suppression of plasma viral load (Brew 2002; own unpublished observations). Even with rapid decrease of plasma viraemia during HAART, many HIVE patients show a significantly protracted decrease of the CSF viral load (Eggers 2003). On these grounds we recommend that in patients with HIVE, the CSF viral load should be determined during the first one or two years of HAART. Modification of the antiviral regimen should be considered when clinical and virologic studies suggest ongoing CNS viral replication with complete suppression of plasma viraemia.

HIV-associated myelopathy

Clinical characteristics

HIV-infected patients may develop a myelopathy without the neuropsychological signs and symptoms of HIVE, labelled HIV associated myelopathy (HIVM). The histopathological hallmark are vacuoles most prominent in the cervical and thoracic parts of the spinal cord and lipid-laden macrophages, hence the term “vacuolar myelopathy” (Petito 1985). These changes are reminiscent of severe combined degeneration and may occur with HIV-negative patients. As HIV viral products have only inconsistently been shown to be part of the lesions, the role of the virus for the disease is uncertain. Pathogenetically, a disturbance of cobalamin-dependent transmethylation has been discussed. Like HIVE, HIVM occurs mainly with advanced immunosuppression. Only a proportion of patients with the autoptic finding of vacuolar myelopathy shows clinically apparent myelopathy during life (dal Pan 1994).

Diagnostic workup

A patient may be suspected of having HIVM if he has a spastic-atactic gait, hyperreflexia with positive Babinski sign, disturbance of sphincter control, erectile dysfunction, and slight signs of sensory dysfunction in a glove and stocking distribution. The diagnosis of an independent HIVM should only be made when a concomitant cognitive impairment is significantly less prominent than the myelopathy. Electrophysiological tests which show increased latencies of somatosensory evoked

potentials (SEP) and the motor evoked potentials on transcranial magnetic stimulation are compatible with the diagnosis. CSF, microbiological and spinal imaging studies are inconspicuous or unspecific, and they have their importance in the exclusion of differential diagnosis, as listed in Table 4. Spinal imaging should include MRI of the cervical and, possibly the thoracic cord.

Table 5: Differential diagnoses of HIV myelopathy and diagnostic workup

condition	adequate diagnostic step (commentary)
Mechanic compression of the myelon (cervical myelopathy, disk herniation)	degenerative changes of the cervical spine MRI shows reduced CSF spaces around the spinal cord with hyperintense lesions of the cord parenchyma
Neurosyphilis	Antibody testing and CSF analysis (pleocytosis >45/3) (serological findings may be atypical for active neurosyphilis)
CMV myelopathy	CSF (signs of inflammation) PCR for CMV in CSF antibody testing in blood and CSF (IgG and antibody index may be increased)
Toxoplasmosis	contrast enhancing cord lesion on MRI
VZV myelitis	CSF (marked inflammatory signs) VZV specific IgG in blood and CSF (IgM may be absent) VZV PCR in CSF Mostly antecedent or accompanying cutaneous zoster lesions
HSV myelitis	CSF (inflammatory signs may be absent), HSV PCR in CSF
HTLV-1 (tropical spastic paraparesis)	travel to the Caribbean, West Africa or East Asia slow evolution of symptoms, bladder dysfunction characteristic, CSF inflammation, HTLV-1 specific antibodies
Severe combined degeneration	Vitamin B12 levels, increased erythrocyte volume
heredo-degenerative diseases (hereditary spastic paraparesis, adrenoleukodystrophy, Friedreich ataxia etc.)	appropriate tests

Treatment

Early observations of significant improvement with zidovudine monotherapy (Oksenhendler 1990) were later confirmed with HAART. This is why any patient with HIVM should be offered effective HAART. A controlled trial showed L-methionin to bring about improvement on electrophysiological but not clinical parameters.

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