
CHAPTER 24

Neurological complications of HIV infection

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Background and objectives

The introduction and widespread use of highly active antiretroviral therapy (HAART) for the treatment of HIV infection has resulted in dramatic reductions in morbidity, mortality, and healthcare utilization [1–3]. Decreasing rates for opportunistic infections, including the neurological infections, have been reported. Diagnostic tools for these neurological complications have been greatly improved in the past 10 years. The therapeutic approach to the neurologic diseases has been influenced by the success of HAART. However, HIV infection has spread in new populations and the neurological complications are still frequent in patients who are not adequately treated and are immunosuppressed. Furthermore, recent studies show that patients who have been infected and/or treated for many years are at risk for developing neurocognitive dysfunction. Alertness, together with neurological knowledge and expertise remain urgently needed. Together, these developments form the main reason for producing these new guidelines.

The objective of the study was to provide neurologists and others with evidence-based guidelines for the diagnosis and treatment of neurological complications of HIV infection.

Neurological complications

These guidelines deal with the most common neurological complications of HIV infection. Although the epidemiology of neurological complications has changed considerably in recent years in the West, the spectrum has remained relatively unchanged. The most frequent opportunistic infections are cerebral toxoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy (PML), tuberculous meningitis, cytomegalovirus (CMV) encephalitis, and CMV polyradiculomyelitis. Primary central nervous system (CNS) lymphoma has become less frequent, but is still an important cause of focal brain disease. The neurological diseases that are more directly related to HIV itself are HIV dementia, vacuolar myelopathy, and peripheral neuropathy. HIV dementia is rare in patients who take HAART, but with resistance and compliance problems patients may become at risk. More subtle cognitive dysfunction is only recently recognized in long-term infected patients. The epidemiology and pathogenesis are not clear yet. It has been suggested that an ongoing chronic infection and immunoactivation play a role. Peripheral neuropathy is still a frequent complication, not only in severely immunosuppressed patients. The role of antiretroviral drugs in the pathogenesis remains uncertain.

HAART

An increasing number of potent antiretroviral drugs are available [4]. When used in combinations of three or four

drugs, this treatment is called HAART. In most HIV-infected patients, especially treatment-naive patients, HAART is effective in rapidly reducing plasma levels of HIV-RNA, accompanied by a gradual increase in CD4 cell counts, sometimes to normal levels [4]. For many antiretroviral-naive patients, CD4 cell counts increase to levels at which the patients are no longer generally susceptible to serious opportunistic infections. As currently available antiretroviral regimens will not eradicate HIV, the goal of therapy is to durably inhibit viral replication so that the patient can attain and maintain an effective immune response to most potential microbial pathogens [5, 6]. The recently updated recommendations of the Working Group of the Office of AIDS Research Advisory Council (OARAC) [7] advise the start of treatment in patients with symptomatic HIV disease and in patients with CD4 cell counts below 350 cells/ μ l or viral loads above 50 000–100 000 copies/ml [6]. The most commonly used regimens to start with contain two nucleoside reverse transcriptase (RT) inhibitors with either a non-nucleoside RT inhibitor or a single (or boosted) protease inhibitor. Antiretroviral activity is evaluated by assessing changes in CD4 cell count and viral load in the plasma. The availability of new drugs has widened the options for patients who fail to respond to their antiretroviral regimen. A patient with one of the neurological complications described below has symptomatic HIV disease and HAART is indicated, but the strength of the evidence for this recommendation varies from complication to complication.

The immune restoration itself, i.e. the result of HAART, may have a beneficial effect on the neurological complication. For some of the neurological diseases (PML, HIV dementia), this has been documented in small, uncontrolled studies. Besides HAART, disease-specific therapy for neurological complications is indicated, as discussed below. The duration of these specific treatments is determined by the level of immunosuppression. Before HAART became available, the treatment for acute infection had to be followed by lifelong secondary prophylaxis to prevent relapses (e.g. for toxoplasmosis, cryptococcosis). The recommendation in general now with HAART is that secondary prophylaxis can be discontinued if CD4 cell counts show a significant and sustained increase in both absolute and percentage terms, for example, if they have increased to above 200 cells/ μ l and have remained at that level for at least 3

months. Primary prophylaxis for neurological complications is not recommended.

Search strategy

A MEDLINE (National Library of Medicine) search of the relevant literature from 1966 to August 2002 was undertaken using various combinations of the following MeSH headings: HIV-1, acquired immunodeficiency syndrome, HIV-infections, toxoplasmosis cerebral, meningitis cryptococcal, leukoencephalopathy progressive multifocal, polyneuropathies, polyradiculopathy, encephalitis, myelitis transverse, lymphoma, central nervous system, cytomegalovirus infection, tuberculosis central nervous system, diagnosis, therapeutics, drug therapy. The following free text words were used: highly active antiretroviral therapy, cerebral toxoplasmosis, PML, CMV encephalitis, CMV polyradiculomyelitis, primary CNS lymphoma, HIV dementia, AIDS dementia, vacuolar myelopathy, HIV myelopathy, and sensory neuropathy. Limitations included meta-analysis, randomized controlled trial, sensitivity and specificity, cohort studies, case control studies.

Grading of recommendations

All members of the task force prepared one or more of the 10 selected neurological complications. The material available from the literature review was integrated and summarized in graded recommendations. The recommendations were approved by all members.

Cerebral toxoplasmosis

Cerebral toxoplasmosis is a frequent cause of focal brain disease in HIV infection. *Toxoplasma gondii* is an obligate intracellular protozoan parasite in human beings. Toxoplasmic encephalitis is almost always caused by reactivation of *Toxoplasma gondii* cysts in brain parenchyma.

Diagnosis

A presumptive diagnosis of cerebral toxoplasmosis in HIV-infected patients is based on: (1) progressive neurological deficits, (2) contrast-enhancing mass lesion(s) on imaging studies [computed tomography/magnetic reso-

nance imaging (CT/MRI)], (3) successful response within 2 weeks to specific treatment (see below) [Class IV]. Absence of one or more of these characteristics makes cerebral toxoplasmosis less likely. Those patients are possible candidates for brain biopsy. In clinical practice, most patients with mass lesion(s) are given 2 weeks of treatment anyway (including patients with negative serology or a single lesion). Cerebrospinal fluid (CSF) studies, including antibody studies and polymerase chain reaction (PCR) studies, have not produced conclusive results [8].

Treatment

Primary therapy for cerebral toxoplasmosis [9–11]: pyrimethamine 200 mg load, then 50 mg/day (oral) with sulfadiazine 1 g four times daily (oral) (or clindamycin intravenous (i.v.) or oral 600 mg four times daily) with folinic acid 10 mg/day (oral) (Class IIa, Level B recommendation).

Other possible combinations include the following.

- 1 Trimethoprim/sulfamethoxazol oral or i.v. 2.5–5 mg/kg (TMP) q.i.d. (Class IIa) [12].
- 2 Pyrimethamine (as above) plus clarithromycin 1 g twice daily (Class III).
- 3 Pyrimethamine (as above) plus azithromycin 600–1800 mg/day (Class III) [13].
- 4 Pyrimethamine (as above) plus dapsone 100 mg/day (Class III).
- 5 Atovaquone 750 mg four times daily (oral) (Class IIa) [14].

For secondary prophylaxis [9, 11]: pyrimethamine 50 mg/day with sulfadiazine 500 mg four times daily (Class IIa, Level B recommendation). Alternatives are: atovaquone 750 mg four times daily (oral) (Class IIa) [15] 13] or pyrimethamine 50 mg/day + sulfadiazine 500 mg four times daily, twice a week (Class IIa) [16].

The primary therapy is usually continued for 6 weeks, followed by secondary prophylaxis. Secondary prophylaxis can be stopped according to the recommendations described above.

Cryptococcal meningitis

Infection with the yeast *Cryptococcus neoformans* in HIV-infected individuals most often leads to a subacute meningitis. The initial infection is a pulmonary infection. In the immunosuppressed host, dissemination occurs afterwards to many organ systems, including the CNS.

Diagnosis

A definitive diagnosis of cryptococcal meningitis is made by using any of the following methods.

- 1 Visualizing the fungus in the CSF using India ink (sensitivity 75–85%) (Class I).
- 2 Detecting cryptococcal antigen by latex agglutination assay in the CSF (sensitivity 95%) (Class I).
- 3 Positive CSF culture for *C. neoformans* (Class I).

Treatment

It is important to be alert (especially in the first week after the diagnosis has been made) for high CSF pressures that may lead to blindness, coma, seizures, etc. [17]. Removing 20–30 ml CSF by (repeated) spinal tap or (in severe cases) a lumbar drain for a few days may be necessary. Based on several randomized clinical trials [18–21] the recommendation for treatment is: amphotericin B 0.7 mg/kg/day i.v. (with or without flucytosine 5-FC; 100 mg/kg/day orally) for 2 weeks (Class Ia). This treatment is followed by: fluconazole 400 mg/day (or itraconazole 400 mg/day) (orally) to complete a course of 10 weeks (Class Ia, Level A recommendation). The addition of flucytosine to amphotericin B did not significantly improve the mortality and clinical course in a randomized clinical trial (RCT); however, flucytosine was well tolerated and there was a trend to a better CSF sterilization with its use in this study [21]. CSF examination should be repeated to confirm a therapeutic response (negative CSF culture).

For secondary prophylaxis fluconazole 200 mg/day (oral) (Class Ia, Level A recommendation; [22–24]. Secondary prophylaxis can be stopped according to the recommendations described above.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a viral opportunistic infection of oligodendrocytes and astrocytes leading to demyelination in the CNS. The causative agent is a polyomavirus named JC virus. JC virus is ubiquitous in human beings and is usually acquired during adolescence (two-thirds have antibodies at age of 14 years).

Diagnosis

Slowly progressive focal neurological deficits with asymmetrical white matter abnormalities on MRI suggest

PML. The lesions are non-enhancing, hyperintense on T2-weighted MRI, without mass effect. The subcortical 'U' fibres are characteristically involved. This diagnosis is strongly supported by positive CSF-PCR for JC virus DNA (sensitivity 72–100%; specificity 92–100%) (Class I) [25]. If the CSF-PCR is negative, it is recommended to repeat CSF-PCR once or twice. Brain biopsy remains the final confirmatory test, but a positive CSF-PCR offers acceptable evidence.

Treatment

In patients who are being treated with HAART, PML arrests or remits in approximately 50%, and survival is prolonged in these patients [5, 26–28].

Studies with cytarabine [29] and cidofovir [30] failed to show any benefit.

CMV encephalitis

Cytomegalovirus belongs to the family of herpes viruses. CMV infection is endemic; the majority of HIV-infected adults have serologic evidence of prior CMV infection. Clinical syndromes in immunosuppressed patients include retinitis, gastrointestinal ulcers, encephalitis, and polyradiculomyelitis.

Diagnosis

CMV encephalitis is suspected in an HIV-infected patient with (usually) a history of CMV disease (e.g. CMV retinitis), a clinically progressive encephalopathy, and periventricular enhancement (ventriculitis) on imaging (CT/MRI) studies. The diagnosis is strongly supported by: (i) positive CSF-PCR for CMV-DNA (sensitivity 62–100%; specificity 89–100%) (Class I) [31] or (ii) positive CSF culture (Class I) [31], but in general CSF viral cultures are highly insensitive.

Brain biopsy is not a realistic option given the brainstem and periventricular localization of the encephalitis. CSF-PCR is the diagnostic test of choice.

Treatment

Induction treatment (for 3 weeks) [32]: ganciclovir 5 mg/kg i.v. twice daily (Class IV) or foscarnet 90 mg/kg i.v. twice daily (Class IV) or cidofovir 5 mg/kg i.v. every week; after two courses every 2 weeks (Class IV) or ganciclovir and foscarnet (dosages as above) (Class IV, Level C recommendation).

Maintenance treatment [32]: ganciclovir 5 mg/kg/day i.v. (Class IV).

CMV polyradiculomyelitis

This is the most common polyradiculomyelitis in AIDS. The most frequent manifestations are pain (low-back, sciatic), paresthesia, sphincter dysfunction, distal sensory loss, and progressive ascending weakness.

Diagnosis

CMV polyradiculomyelitis is suspected in an HIV-infected patient with (usually) a history of CMV disease (e.g. CMV retinitis), clinically a rapidly ascending polyradiculomyelitis and a highly characteristic CSF polymorphonuclear pleocytosis. The diagnosis is strongly supported by: (i) positive CSF-PCR for CMV-DNA (sensitivity 62–100%; specificity 89–100%) (Class I) [31] or (ii) positive CSF culture (Class I) [31], but in general CSF viral cultures are highly insensitive.

Treatment

Induction treatment (for 3 weeks) [32]: ganciclovir 5 mg/kg i.v. b.i.d. (Class IV) or foscarnet 90 mg/kg i.v. b.i.d. (Class IV) or cidofovir 5 mg/kg i.v. every week; after two courses every 2 weeks (Class IV) or ganciclovir and foscarnet (dosages as above) (Class IV, Level C recommendation).

Maintenance treatment [32]: ganciclovir 5 mg/kg/day i.v. (Class IV).

Tuberculous meningitis

Infection with *Mycobacterium tuberculosis* is the leading cause of death worldwide among persons infected with HIV. Tuberculous meningitis and CNS tuberculomas are common complications. CNS tuberculosis in HIV disease is more frequent in developing countries.

Diagnosis

CNS tuberculosis has been described in 10–20% of patients with HIV-related tuberculosis. Lymphocytic pleocytosis, low glucose, and raised protein are the typical features of tuberculous meningitis. Post-contrast brain scans show enhancement of the meninges and the periphery of the tuberculoma and, on occasion, may reveal miliary lesions. Hydrocephalus may appear early. The diagnosis is based on demonstration of *Mycobacterium tuberculosis* in the CSF [33, 34]: (i) culture (sensitiv-

ity 25–86%) (Class I); (ii) CSF smear (ZN) (sensitivity 8–86%) (Class IV); or (iii) CSF-PCR (sensitivity 83–100%; specificity 88–100%) (Class II).

Treatment

Isoniazid 5 mg/kg/day, up to 300 mg/day, and rifampicin 10 mg/kg/day, up to 600 mg/day, and pyrazinamide 15–30 mg/kg/day (max 2.5 g/day), and ethambutol 15–25 mg/kg/day, up to 1600 mg/day (Class III, Level A recommendation; [33, 34].

Ethambutol can be substituted with streptomycin (15 mg/kg/day, up to 1 g/day i.m. or i.v.; max 2 months) or amikacin (15 mg/kg/day i.m. or i.v.). The role of steroids in HIV-positive tuberculous meningitis is unclear. The minimum duration of treatment is 6 months. Isoniazid may lead to pyridoxine deficiency and a sensorimotor distal polyneuropathy. Therefore pyridoxine 20 mg/day should be added to the regimen.

Primary CNS lymphoma

Primary CNS lymphoma is a non-Hodgkin's lymphoma that arises within and is confined to the nervous system. It is the second most frequent CNS mass lesion in adults with AIDS in Western countries. Primary CNS lymphoma is associated with Epstein–Barr virus (EBV) infection. The transforming potential of the virus plays a role in the pathogenesis of this tumour. With the introduction of HAART the incidence has declined [35, 36].

Diagnosis

A definitive diagnosis is made by histological examination of brain tissue (obtained by brain biopsy or at autopsy). In an HIV-infected individual with a single or multiple contrast-enhancing brain lesion(s) on CT or MRI not responding to anti-toxoplasmic therapy, a presumptive diagnosis can be supported by: positive CSF EBV-PCR (sensitivity 83–100%, specificity 93–100%) (Class II) [37–40]. Cytological examination of the CSF rarely reveals pathological cells and its value, although not well studied, seems limited. Data on other potential CSF markers of primary CNS lymphoma are inconclusive. SPECT/PET study results are inconclusive, and these investigations cannot be recommended.

Treatment

HAART improves neurological status and prolongs survival in patients with primary CNS lymphoma [41]. Besides HAART three other treatment options exist: (i)

whole-brain irradiation and corticosteroids (Class III) [42–44]; (ii) intravenous methotrexate followed by whole brain radiation (Class III) [45]; and (iii) methotrexate, thiotepea, and procarbazine intravenously in combination with methotrexate intrathecally (Class III, Level B recommendation; [46].

HIV dementia

HIV dementia is a syndrome of cognitive and motor dysfunction that has also been termed: AIDS dementia complex, HIV-associated cognitive-motor complex, HIV-associated dementia, and AIDS dementia. Its paediatric counterpart is called progressive encephalopathy. The cognitive impairment is compatible with a subcortical dementia. Most patients with HIV dementia are severely immunosuppressed.

Diagnosis

The diagnosis is based on: (i) progressive cognitive impairment (with or without motor dysfunction); (ii) exclusion of CNS opportunistic infections and tumours (by CSF and CT/MRI) [47, 48] and is supported by: (1) high levels of HIV RNA in the CSF (above three log copies/ml) (Class III) [49–51] and (2) diffuse, bilateral (often symmetrical) non-enhancing white-matter hyperintensities on MRI (Class III) [52].

Treatment

Class III evidence for HAART [53, 54] leads to a Level B recommendation. Most nucleosides and non-nucleosides (e.g. nevirapine) penetrate relatively well into the CSF; most protease inhibitors do not (with the exception of indinavir). It seems reasonable to include at least two drugs in the regimen that penetrate well [55]. The data are still limited. Most combinations have not been well studied in HIV dementia.

HIV myelopathy

Spinal cord disease is observed in various stages of HIV infection. The most common type is HIV myelopathy (also named HIV-related vacuolar myelopathy). HIV myelopathy is a progressive non-segmental spinal cord disease. The diagnosis is one of exclusion.

Diagnosis

The diagnosis is based on: (i) progressive myelopathy without sensory level; (ii) absence of focal lesion or mass

lesion in spinal cord or compression of spinal cord on MRI; (iii) negative human T-cell lymphotropic virus (HTLV-I) serology; (iv) normal serum vitamin B12; (v) negative CSF PCR for herpesviruses; (vi) negative CSF syphilis tests [56, 57]. All diagnostic tests have only Class IV evidence.

Treatment

HAART (Class III) [58, 59].

HIV polyneuropathy

Polyneuropathies do occur frequently in the course of HIV infection. The pathogenesis is poorly understood and treatment is largely restricted to symptomatic pain therapy.

Diagnosis

The most important neuropathy in HIV infection is the distal sensory polyneuropathy. Its pathogenesis is unclear. This neuropathy is indistinguishable from the toxic neuropathy caused by the nucleosides zalcitabine, didanosine, and stavudine. Symptoms of paraesthesiae and pain predominate; disability caused by loss of sensory or motor function is less prominent. Electrodiagnostic studies may be helpful in confirming the diagnosis but may not be necessary in all cases.

Treatment

Symptomatic treatment: (i) amitriptyline 25–100 mg/day (Class I); (ii) tramadol 50 mg three times daily to 100 mg four times daily (Class I); (iii) carbamazepine 200 mg three or four times daily (Class I) [60] and lamotrigine (Class I) [61]. Gabapentin is a promising drug (2400–3600 mg/day), but has not been studied in RCT.

Immune reconstitution inflammatory syndrome (IRIS)

IRIS has been recognized after the introduction of HAART. Due to an enhanced immune response as a result of an improved immunity after starting HAART, a paradoxical progression (clinically and radiologically) of neurological opportunistic infections may occur. IRIS has been described in PML, toxoplasmosis, cryptococcal meningitis, and VZV-infections. Although studies are lacking, some patients do respond to a brief course of corticosteroids [62].

Summary and conclusions

Despite the success of HAART, HIV-infected individuals are at risk for a variety of neurological complications. The risk for those complications increases with an increasing level of immunodeficiency. Those patients with CD4 cell counts below $200 \times 10^6/\text{ml}$ are particularly at risk for opportunistic infections, lymphoma, and HIV dementia. Nucleic acid amplification in the CSF by PCR has greatly improved the diagnostic accuracy in PML, CMV infections, primary CNS lymphoma, and HIV dementia. Besides HAART, specific treatment options are available for the majority of these complications. In general, the task force recommends rapidity in evaluating these patients to limit damage to the nervous system.

Conflicts of interest

The authors have reported no conflicts of interests.

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