Etiologic spectrum

The spectrum of neurological affection of CNS occurring during HIV infection is wide. They are divided into three groups according to their etiologies, HIV-related affections, those related to OI and brain tumors.

HIV-Related Neurological Afections

Neurological manifestations of primary HIV infection

Neurological manifestations of primary infection are the consequence of early invasion of the CNS by HIV during seroconversion [12]. They are observed in 10% of cases [13]. Are varied and are a sign of gravity [14]. These are meningitis, meningoradiculitis, meningoencephalitis, meningomyelitis, and acute polynynepathy. Evolution is usually a spontaneous resolution. Diagnostic tests detecting both the presence of p24 antigen and antibodies by Elisa method allows, except during the first 15 days after the contagion, the diagnosis. Treatment of primary infection is based on the ARV therapy [13].

HIV encephalitis

Encephalitis or HIV-related dementia is currently the most common neurological condition in the HIV infection [2,13-16]. Its relative impact compared to other complications increased after the arrival of ART. Its absolute incidence, however, was divided by 10, as for opportunistic infections [2]. The multicenter AIDS Cohort Study found a prevalence of 0.4%, while other retrospective studies have reported a prevalence of 7.5% to 27%. In a study conducted in India, HIV dementia was the most common cause of CNS affection (33.65%), followed by the OI, 21.63% [16]. Pathophysiological mechanisms responsible are subject to a number of assumptions including the action of inflammation, the role of infected macrophage or direct infection of nerve cells. HIV-related encephalitis can be observed in case of failure immunovirological ART in an immunocompromised patient (CD4 less than 200 / mm3) or affect a patient with well controlled systemic infection but whose CNS viral infection is manifestly away, or to which it is resistant [2]. Clinical expression can range from a simple psychomotor retardation associated with memory impairment and balance to an array of more advanced sub-cortico-frontal cognitive impairment with apragmatism or even akinetic mutism [2,13]. The presentation can also be acute in form of seizures or psychiatric manic or delusion [2,13]. Diagnosis is based on a set of clinical, biological and [2,13,14] imagery. In 2007, the HIV bihavioral Neuro Research Center (HNRC) proposed revising the 1991 criteria to group cognitive disorders associated with HIV in a general term HIV-Associated Neurocognitive Disorders (HAND) and set three diagnostic classes of increasing severity: asymptomatic cognitive impairment, secondly, mild cognitive impairment and ultimately dementia associated with HIV [17]. Brain MRI; key consideration; highlights anomalies;often diffuse and poorly limited of the supratentorial periventricular white matter (WM) (Figure 1) [2,13,15]. The study of cerebrospinal fluid (CSF) is often normal;
or shows moderate or specific abnormalities (discrete elevations of the protein level, the presence of some normal lymphocytes) [15]. The management is based on ART favoring molecules; those pass well through the blood brain barrier; take into account the resistance profile and are easy to take to improve adherence to treatment [18].

**Vacuolar Myelopathy**

Vacuolar myelopathy is the most frequent myelopathy occurring during HIV infection, its prevalence varies from 20 to 55% according to autopsy series [7]. Its incidence is low [2]. It results from the intramyelinic vacuolation of the spinal cord [7]. It can be isolated or affect a patient with HIV encephalitis. Its diagnosis is pathological and remains elimination [2]. The clinical presentation is polymorphous and some histologically confirmed myelopathies remain asymptomatic. Clinical signs, which are typical only at the severe stage of the disease, are those of a spastic paraparesis with proprorceptive ataxia and occasionally genito-sphincter and erection disorders [7]. Clinical diagnostic criteria have been proposed by the American Academy of Neurology AIDS. The spinal cord MRI, whose interest is primarily to eliminate other causes of myelopathy, is usually normal. More rarely, it highlights T2 hyperintensities located mainly in the posterior columns. Sometimes in older and/or severe, the marrow is atrophic. Lumbar puncture (LP) is usually normal [7]. Treatment is based on ART that cross the hemato-encephalic barrier, always associated with symptomatic treatment (physical therapy, vitamin B12, analgesics and muscle relaxants) [7].

**B. CNS infections**

CNS infections are present in 17.9% to 21.6% according to studies. Their main causes are cerebral toxoplasmosis, tuberculous meningo-encephalitis, meningeval cryptococcosis and progressive multifocal leukoencephalopathy.

**Cerebral Toxoplasmosis (CT)**

The CT is the most common CNSOI during HIV infection. Its prevalence varies from 15 to 30% [19,20]. It occurs in immunocompromised patients (lower CD4 <200/mm3), with a positive toxoplasmosis serology and not receiving specific chemoprophylaxis [3-6,13,21,22]. CT that occurs within the context of an inflammatory immune reconstitution syndrome (IRIS) is described [22]. Histologically, the toxoplasma abscesses are characterized by a necrotic center surrounded by cellular inflammation comprised of lymphocytes and macrophages [23]. Clinically, CT is manifested by headaches with focal neurologic signs (deficiency, seizures) fairly quickly evolving [23]. The brain scan; easier to obtain in an emergency; shows multiple abscesses located in the basal ganglia and subcortical regions, taking a ring contrast, associated with perilesional edema; all making a rosette appearance (Figure 2) [24]. MRI, examination of choice; the elementary lesion translates in T1 sequence by hypointense, mass effect on surrounding structures, corresponding to the lesion and its edema. In sequenceT2 by hyperintensity, containing a hypointensity zone [23,25]. The use of PCR to search the DNA of Toxoplasma gondii in CSF has become promising [25]. Its specificity was 100% and its sensitivity varies from 16.7 to 100%. Even if PCR is negative, the diagnosis cannot be excluded. Isolated bone marrow involvement or associated with brain damage is rare. It results in an acute paraparetic or paraplegic manifestations, associated with sensory or sphincter disorders [25]. CT is the first cause of death by neurological condition associated with HIV (40.8%), hence emergency antitoxoplasmic treatment should be started before any intracranial expansive process (IEP) in a patient with HIV for two weeks [6,13]. The response to presumptive treatment is the major diagnosis argument [19,21,23,25]. The persistence of the images or their aggravation should make one consider other diagnoses such as lymphoma and push the clinician to do the LP, PCR and brain biopsy [3,26]. The standard treatment is a combination of pyrimethamine (100 mg on day 1 and 1 mg/kg/day or 50 to 75 mg/d maintenance) and sulfadiazine (100 mg/kg/day divided into 4 doses with a maximum of 6 g/d), folinic acid (25 mg/day) is added to prevent the hematological toxicity of pyrimethamine [27,28]. The trimethoprim (10 mg/kg/day) - sulfamethoxazole (50 mg/kg/day) has shown efficacy as a treatment of attack and is a therapeutic alternative in developing countries [28]. The treatment duration is at least 6 weeks and until clinical and radiological response [3]. The ART treatment should be started within the first two weeks of the attack treatment [28]. Preferred maintenance therapy is cotrimoxazole at a dose of 960 mg/day given its antitoxoplasmic and antineumocystic effectiveness. It must be maintained until the increase of the T cell rate CD4 beyond 200/mm3 for at least six months [3]. Corticosteroid therapy has not proven effective in the treatment of perilesional edema [27]. Primary prevention is indicated in all patients infected with HIV with a lymphocytes T CD4 count below 200 mm3 [3]. It includes a daily intake of a cotrimoxazole prophylaxis (800/400). In the absence of CD4, Toxoplasma gondii antibodies, dietary advice and hygiene must be reminded to avoid seroconversion which should be sought annually in immunocompromised patients (CD4 <200/mm3) [27].

**Tuberculous Meningitis**

CNS affection by Mycobacterium tuberculosis and its prognosis is not modified by HIV infection [7]. Tuberculous (TB) meningitis is the main etiology of lymphocytic meningitis in patients infected with HIV in Africa [29,30]. It usually appears at an early stage of the disease (CD4 between 200 and 500/mm3) and is manifested by encephalitic signs occurring in an infectious context [23,18]. Brain imaging shows a contrast and/or dilation of cerebral ventricles, an evidence of hydrocephalus [12]. CSF is typically clear, with high lymphocyte level, hypoglycorrhachia and protein level is usually greater 1G/l [12]. In severe immunosuppression, CSF may be atypical [13]. KB PCR in CSF is a means of rapid and specific diagnosis, but lacks sensitivity [12]. The data on focal CNS tuberculosis (tuberculoma, abscess) associated with HIV is limited. [31] However, some studies suggest the existence of a correlation between the appearance of tuberculosis and HIV infection of the brain. They are manifested by focal neurological signs that depend on their location [23]. In imaging, Tuberculomas are rounded formations, multiple, small size, which takes a nodular crown image after injection of contrast product (Figure 3) [23,33]. They sit at the junction of the WM and the gray matter (GM), in the region of the basal ganglia of the base and the brain stem. They can also be quite numerous, realizing cerebral miliary [23]. Histologically, the tuberculoma consists of a central necrosis surrounded by granulomatous infiltration made of lymphocytes, epithelioid and giant cells and collagen sclerosis [23,25]. Bone marrow involvement is frequently observed during HIV infection [16,30]. Mortality related to CNS TB seems higher in case of HIV infection [2,36]. TB treatment is as recommended in non-HIV-infected patients and is based on quadruple therapy (isoniazid, rifampicin, pyrazinamide, ethambutol) for 2 months followed by combination therapy (isoniazid, rifampicin) for 7 to 10 months. In meningeval affection, it is recommended to use a corticosteroid therapy 1 mg / kg / day, it improves the prognosis [3,27]. As part of IRIS, tuberculous meningitis is frequent and serious. His impact could be reduced by delayed introduction of ART, especially when there are risk factors for IRIS like positive CSF culture. It is necessary; to wait for at least 4 weeks subject to clinical and laboratory improvement before introducing ART and not to ignore another associatedOI [27].

**Figure 1:** Cerebral MRI T2 FLAIR: Puncture and nodular hyperintensities in cerebral peduncle and left cerebellar hemisphere in favor of HIV encephalitis.

**Figure 2:** CT axial cut: bilateral fronto parietal hypodensities enhanced nodular way related to toxoplasma abscess.

**Figure 3:** Nodular periventricular hyperintensities taking contrast after injection of gadolinium evoking tuberculomas.

**Figure 4:** MRI FLAIR sequence: Hyperintensities in cortico-cortical level in left occipital for PML.
TB treatment in the context of HIV infection, is firstly drug interactions between ART and rifampicin, and secondly, the risk of paradoxical worsening of TB lesions after introduction of ART. A combination comprising efavirenz at a dose of 600 mg / day should be preferred. Integrase inhibitors appear to be an interesting therapeutic option because of the absence of metabolism via cytochrome P450. Finally, if the ARV treatment should include protease inhibitors, rifampin is replaced with rifabutin (150 mg/48 h)[35].

Cryptococcal neuromeningitis (CNM)

CNM affects 2-30% of patients infected with HIV by region, primarily affecting patients with profound immune deficiency with CD4 <50/mm³ unaware of their HIV status [36]. It is manifested by meningoencephalitis with basilar impairment and affection of cortical GM in the vast majority of cases (70–90% of cases) [37]. The franc meningeal syndrome is rare, found in less than 40% and rarely complete [38]. The febrile neurological syndrome is more evocative. Motor deficits are suggestive of brain cryptococcoma [39]. The spinal cryptococcosis is exceptional, in form of abscesses, but it is mainly the complications in the form of arachnoiditis that are described [40]. The CNM is an emergency diagnosis. Diagnosis is based on CSF examination after staining with India ink, culture and detection of capsular polysaccharide by agglutination of latex particles [41]. The extension examination is always required [30]. It assesses the initial prognosis and guides the choice of treatment protocol [43]. Radiological aspect of the CNM is extremely polymorphic, without any specificity. Brain MRI is mostly normal but its useful in order to eliminate other diagnoses. Dilatation of Virchow Robin spaces is highly suggestive of cryptococcosis [40]. The CNM is a severe OI. It is the third cause of mortality attaining up to 44% of CNS disease during HIV infection despite antifungal treatment and ART [37,41,44]. The treatment of choice is based on an attack treatment involving amphotericin B (0.7 to 1 mg / kg / day) and flucytosine (100 mg/kg/day) for two weeks. Favorable development requires a relay with fluconazole (400 mg/d oral intake) for 8 weeks minimum or until sterilization mycological cultures [43]. If contraindication of fluconazole, itraconazole (400 mg/d) represents an alternative, although its effectiveness is less than that of fluconazole. The use of lipid formulations of amphotericin B (AmBisome) gave good results at a dose of 4 mg / kg / day [6]. The LP discharge should be performed 2 to 3 times per week if the CSF opening pressure is greater than 25 cmH2O [41]. Control of intracranial hypertension is a major element of prognosis [30]. ART treatment should be started early, within a period of about one month after the start of antifungal treatment to prevent the occurrence of other OI, but it must consider the risk of IRIS [40]. Prophylactic treatment relapse is systematic as immune reconstitution was not obtained by the ART. It will be started after the tenth week of the attack treatment based on fluconazole dosage which will be reduced to 200 mg/d. This prophylaxis is stopped in patients receiving effective ART (CD4> 100 cells/mm³ and undetectable viral charge) for more than three months [38,39,45].

Progressive Multifocal Leukoencephalopathy (PMLE)

It is a subacute demyelinating disease of the WM whose causative agent is a polyomavirus, mainly JC virus [7]. It occurs at the stage of severe immunosuppression (CD4 less than 100/mm³) [7,13,21,46,47]. Its frequency has declined significantly since the introduction of ART, it is estimated at 5% [21,46,47]. Clinically, the PML is characterized by a focal neurological deficit of subacute evolution [21,23]. Visual disorders reveal 30-45% of the cases. Sensory disorders (10–20%) are also noted. Seizures, sometimes inaugural, often complicate the advanced forms of the disease [7].
Some observations of meningencephalomyelitis JC virus have been reported in association with HIV [7]. Diagnosis is most commonly achieved through imaging data and biology [46]. Brain MRI is highly suggestive when showing hyperintense lesions on T2 or hypointense on T1. After injection, these lesions will not be enhanced in most cases (Figure 4) [7,23]. The parietal-occipital and frontal regions are more frequently affected [2,7,23,46-48]. The diagnosis can be confirmed by detecting the viral genome in the CSF by PCR, which has a high specificity (100%) but and a sensitivity of 80% [7,23,46]. The clinical and radio-biological criteria may be sufficient to retain the PML [7]. Very rarely, we must resort to brain biopsy to confirm the diagnosis [23]. PML remains a severe disease with poor prognosis, for which it is necessary to evaluate new therapeutic protocols [46]. It progresses in the vast majority of cases to an inevitable aggravation and death occurs on average in 6 months [7,46,49]. There is currently no specific treatment for the JC virus has proved its effectiveness. The treatment is based on, as soon as possible, an effective ART treatment. The use of intensified pentamethyridinon is potentially interesting although not completely validated [7,46,49]. Sometimes, multitherapy is ineffective on the progression of PML despite a good immunovirological response and sometimes fatal aggressions with immune restoration are reported [46]. The only preventive treatment of PML is effective ART treatment [27].

**Neurosyphilis**

Syphilis is common in patients infected with HIV due to the sexually transmitted nature of both infections [3,5]. Its prevalence is ten times that of the general population [2,5]. The natural history of syphilis seems to be affected by HIV infection and cases of neurosyphilis are more common in this population [50]. Approximately 35% of subjects with secondary syphilis have asymptomatic neurological affection highlighted by the CSF study and many cases of neurosyphilis have been reported in patients treated for early syphilis. The hypothesis made is that of reinfection or poor therapeutic compliance related to immune deficiency [7]. The neurological affection may occur at all stages of the disease, it is independent of the immune status [2,7,51]. Clinical manifestations include menigitis, the meningoarterial, general paralysis and tabes. The usual presentation is that of usually lymphocytic meninigionis, symptomatic or not, eventually associated with uveitis, the cranial nerves affection and / or ischemic stroke [7]. Rarer forms of neurosyphilis like gums, meningo-myelitis, lumbosacral polyradiculopathy are noted in HIV infection [3,5,7]. Brain imagery may reveal abnormalities of WM, meningeal contrast, infarctions and / or arteritis in the basal ganglia and the sylvian territory and gums (cortical nodules that take contrast). The diagnosis of neurosyphilis is difficult because CSF anomalies are non-specific [7]. Interpretation of the results of the LP requires a simultaneous assessment of plasma serology. The arguments for neurosyphilis are elevated protein level in CSF, hypercyctosis (20 elements), positive VDRL or FTA IgM+positif CSF [25]. Treatment is IV administration of penicillin G (20 MU/day) for 10 to 14 days [3]. Ceftriazone (2 g/day) for 10 to 14 days is less validated [27]. Prolonged clinical and serological monitoring is done because of the risk of re-infection [7].

**CMV Encephalitis**

CMV encephalitis has become extremely rare in HIV infection [13]. It occurs at the stage of severe immunosuppression (CD4 <50 cells/mm3) [2]. The clinical presentation is that of febrile encephalitis. There are no specific CT scan signs.Perciventricular hypodensities are evocative [18]. The LP is normal or shows nonspecific abnormalities [12]. Myelitis associated with CMV is frequently associated with peripheral neurological affections while realizing a myeloradiculitis presentation. They can be focal and necrotizing or extended [12,23]. The spinal MRI shows in the first case a lesion hypointense on T1, taking contrast in periphery, quite evocative and in the second case an intramedullary hyperintensity and T2 which is not specific (Figure 5). It may also be normal [7]. The diagnosis is mainly based on the CMV PCR positive CSF, the existence of extra-neurological locations related to CMV and the absence of other causes, but sometimes it’s triall therapeutic that permits CMV encephalitis diagnosis [7]. This condition is of extremely poor prognosis, it requires emergency treatment [2,13]. It is based on three molecules: ganciclovir (5 mg / kg / 12 hours), foscarit (90 mg/kg/12 hours) and in second-line, cidofovir (5 mg/kg/week). The combination of 2 molecules seems more effective than mono therapy [3]. After initial treatment of 4-8 weeks, maintenance treatment takes over until the increase of CD4 levels above 100 cells / mm3 [52]. ART treatment should be started within the first weeks of treatment [53].

**Primary Brain Lymphoma (PBL)**

Lymphoma remains a major complication of HIV infection and the second leading cause of cancer death in this population at least in the western countries.PBL represents less than 5% of non-Hodgkin lymphoma [54]. Its incidence has decreased dramatically in the late 1990s, then increased again over the last decade. This is to be compared with the increase in the incidence of lymphoma in immunocompetent subjects [51]. There are two forms in which the pathophysiology and treatment are closely linked. The form occurring in patients with profound immunodeficiency, associated with the Epstein-Barr virus (EBV), for which immune reconstitution plays a crucial role and may even be sufficient to achieve remission. Rare cases (30%) occur in patients with controlled HIV infection with a CD4 count >100/mm3 [27]. The neurological symptoms are that of an expansive intracranial process [13]. Brain MRI is the standard imaging. It is useful for diagnosis, monitoring evolution and in particular to differentiate it from a CT [14]. The typical appearance is that of an expansive process taking the contrast intensely and evenly, “snowball” (Figure 6). The lesion may be infra or supratentorial, uni- or multifocal [51]. Large tumor size and crossing of the centerline are often used as criteria in favour of lymphoma [51]. The other arguments are the predominant periventricular location, invasion of ventricular horn, the heterogeneous appearance of the contrast product, perilesional edema often greater than 3 cm. [14] Differential diagnoses are numerous, represented by other brain tumors: Mainly gliomas in the first place, but also the differential diagnosis with (cranial tumours) CT is difficult. The definitive diagnosis is based on histology [51]. It is large B cells diffuse lymphoma in over 90% of cases [7,51]. Burkitt's NHL is also frequent in patients with HIV infection and so is systemic locations [51]. EBV is almost always found in the biopsies. Viral charge in the blood, like in the CSF, may be high. A value greater than 2000 copies/mL in CSF have a specificity of 100% and a sensitivity of 70% [55]. The diagnosis is difficult and therefore late, which makes the prognosis worse than lymphoma in patient not infected with HIV [2,13]. The general condition is a major prognostic factor [56]. Improved immunity is beneficial. Some patients have even got prolonged complete remissions with only the implementation of ART [51]. In profoundly immunosuppressed patients, treatment is based on a short treatment to control the lymphoma at the same time as the introduction or optimization of ART. Two to four cycles involving high-dose corticosteroids and Methotreex or Aracytine may suffice before letting immune reconstitution obtain remission and six cycles are required in patients with controlled HIV infection [27,51]. Brain radiotherapy, poorly tolerated in this context, is now reserved only for resistant lymphoma [27]. Control of viral replea
-tion by ART is associated with a significant improvement in patients treated for lymphoma [54].

**Stroke**

The prevalence of stroke in patients with HIV infection is multiplied by 10 compared to the general population in comparable age groups and associated with higher mortality. There is a predominance of ischemic stroke [2]. Its main causes are cardiac embolism, infectious vasculitis (tuberculosis, CMV, HSV, syphilis, cryptococcosis, candidiasis, CT), vasculitis associated with the PBL and disorders of hemostasis (antiphospholipids antibodies, protein S deficiency, DIC). In 25-40% of cases, no specific cause is found and cryptogenic stroke diagnosis is retained. Other causes are angiopathy associated with HIV and early atherosclerosis, probable side effects of ARVs. Immune restoration could also be responsible for cerebral vasculitis [2,7,13,29,57,58].

**Conclusion**

Neurological complications are frequent and serious during HIV infection. They require early diagnosis and appropriate treatment in order to avoid delayed treatment corollary of a very high mortality. The clinician should also be aware of the interest of tracking HIV infection before any neurological event.

**References**


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