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HIV Associated Neuropathies

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1. Introduction

Over the past decade there have been significant demographic changes in the HIV epidemic. The overall population of people living with HIV/AIDS is aging. The effect of HAART, aging and resulting comorbidities, such as hypertension, and diabetes add new complexity to HIV and related conditions such as HIV neuropathies.

HIV-associated polyneuropathy is still the most common neurological complication of HIV infection and is one of the main risk factors for development of a neuropathy worldwide. Many types of peripheral neuropathies are seen in HIV infection depending on the stage of infection. The inflammatory demyelinating neuropathies both acute (Guillain-Barré syndrome [GBS] and chronic (chronic inflammatory demyelinating neuropathy [CIDP] occur mainly at the time of seroconversion or early in the course of the disease while syndromes associated with opportunistic infections like CMV (i.e. polyradiculoneuropathy) occur in the late phase of HIV infection and are related to the loss of immune function. The most common neuropathy in HIV-infected patients is the sensory HIV associated neuropathy which includes distal symmetrical polyneuropathy (DSP) and antiretroviral toxic neuropathy (ATN). Those patients may experience painful symptoms such as burning or hyperalgesia in the feet and treatment is very often focussed on management of neuropathic pain. However one should be aware that the high prevalence of HIV-DSP in the HIV population makes the coexistence of more than one neuropathic condition likely either because of comorbidities or aging. These complexities have led to neuropathic syndromes that do not meet diagnostic criteria because of overlapping syndromes. We review the clinical manifestations, epidemiology, clinical diagnostics, and pathophysiology as well as management strategies for HIV-associated polyneuropathies.

2. Diagnostic evaluation

One way to classify HIV-neuropathies is according to the stage of HIV disease in which they occur. Therefore it is mandatory to have an actual CD4 cell count. Some types of neuropathies such as inflammatory demyelinating neuropathies often occur during seroconversion, before strong immunosuppression [1-4] while others such as progressive polyradiculopathies associated with CMV infection are common in late stages of AIDS.

Over the past decade there have also been significant demographic changes in the HIV population, which has consequently brought attention to common so called "age related neuropathies" now also occurring in the HIV population. Figure 1 summarizes laboratory

parameters that are recommended as a baseline diagnostic in patients representing with the clinical symptoms of neuropathy.

erythrocyte sedimentation rate or C-reactive protein, complete blood count, comprehensive metabolic panel (blood glucose or glucose tolerance testing (GTT), renal function, liver function), thyroid function tests, serum B12 (serum methylmalonic acid with or without homocysteine for low normal vitamin B12 levels), serum immunofixation electrophoresis, hepatitis B and C panel, Treponema pallidum screening test, immune status, HIV viral load, antinuclear antigen profile. In case of a co infection with hepatitis C: cryoglobulins.

Fig. 1. Basic laboratory parameters in HIV-infected patients presenting with distal symmetric neuropathy.

Cerebrospinal fluid (CSF) analysis is usually acquired when an inflammatory or an opportunistic/neoplastic neuropathy is suspected. You have to be aware that it may reveal confusing results in cases of GBS or CIDP, which occur mainly in patients with high CD4 counts. This is because asymptomatic HIV patients may show an elevated protein and a mild lymphocytic pleocytosis [1, 2]. CSF analysis is however very important in patients with CD4 counts below 200/ μl in whom there is a strong suspicion of an underlying infectious or malignant etiology.

2.1 Functional and morphological assessment of nerve fibers

Neurophysiological examination has to be done in every patient presenting with neuropathic symptoms in order to classify the neuropathy as either axonal or demyelinating and to assess a subclinical large fiber involvement in patients presenting with typical small fiber symptoms such as burning, aching or stabbing pain mainly localized in the feet. Somatosensory evoked potential may be useful if a myelopathy is suspected.

HIV-infected patients represent very often with a pure small fiber neuropathy with burning feet, which may be difficult to objectify because of a paucity of clinical signs and unremarkable electrodiagnostic studies. Advances have been made in identifying those patients during the last decade. Skin biopsy from the distal leg and assessment of epidermal nerve fiber density (ENFD) using antibodies to protein-gene product 9.5 is nowadays a validated tool [5, 6]. ENFD declines with age [7], which has to be taken into account with the increased aging of HIV-infected individuals. Beyond skin biopsy, functional measurements are applicable such as quantitative sensory testing or contact heat-evoked potentials (CHEP's) the later evaluating late potentials of A-delta and C fibers at the scalp following cutaneous stimulation. It has been shown that by using CHEP's the sensitivity to detect patients with predominant small fiber involvement is higher compared to conventional electrodiagnostic techniques [8].

2.2 Nerve biopsy

Nerve and muscle biopsies are only required in selected cases especially in patients representing with rapid progressing neuropathies. Reasons to perform a biopsy are patients where vasculitis, amyloidosis or storage diseases are suspected. Neuropathic pain on the biopsy site remains in 10 to 20 % of the patients.

3. Subtypes of HIV-associated neuropathies

HIV-associated neuropathies can be classified according to clinical, neurophysiological or histomorphological criteria. Figure 2 summarizes the HIV-associated subtypes.

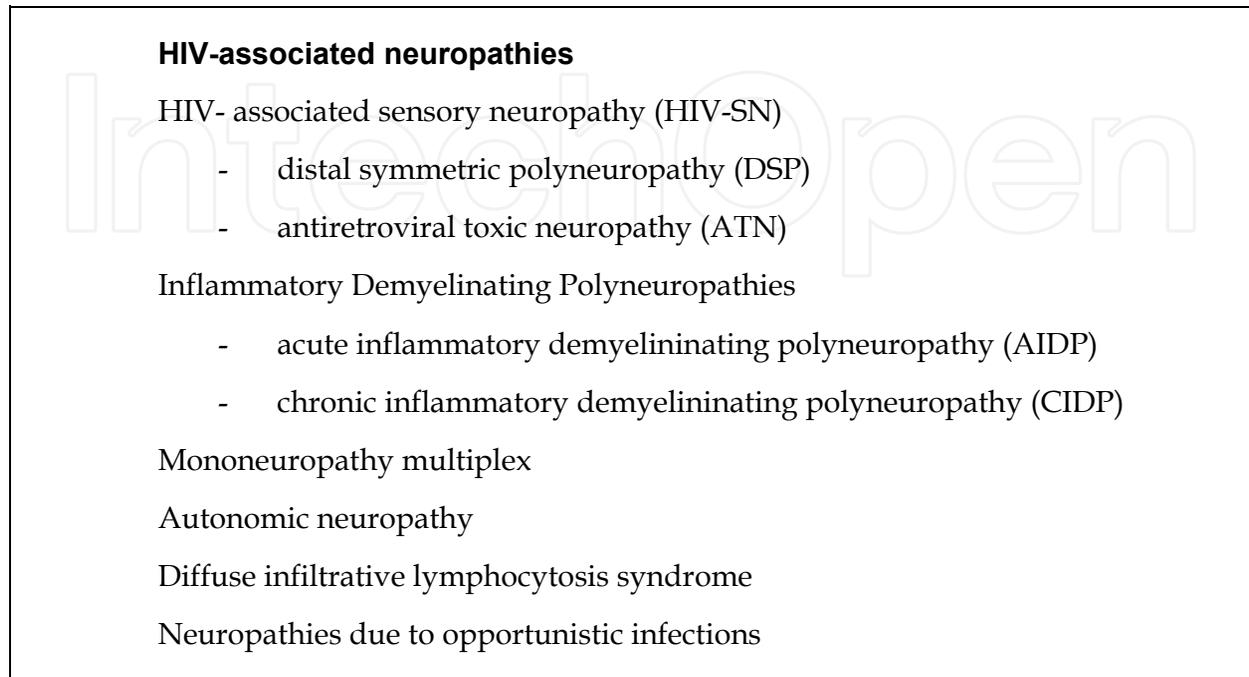


Fig. 2. HIV-associated neuropathies.

4. HIV-associated sensory neuropathy (HIV-SN)

HIV-SN is by far the most common neurological complication in HIV infection [9, 10]. HIV-SN summarizes 2 subtypes that are clinically undistinguishable: distal symmetric polyneuropathy (DSP) which occurs mainly during advanced stages of HIV infection and antiretroviral toxic neuropathy (ATN) as a result of neurotoxic antiretroviral treatment.

4.1 Epidemiology

The prevalence of HIV-SN has been found to increase further. In various cohorts, its prevalence reaches up to 50% [11, 12]. Early epidemiological studies conducted during the pre HAART-era describe an annual incidence of 36% for HIV-SN compared to 21% in the HAART-era [11, 13]. The increasing life expectancy of HIV-infected individuals and the high cumulative dosage of neurotoxic antiretroviral substances, in particular ddC, ddI and d4T, represent the causes for the increasing prevalence [14]. Markers of advanced HIV disease such as low CD4 cell count (especially a CD4 nadir below 50 cells/ μ l), a high HIV viral load (> 10.000 cop./ ml) as well as a diabetes and demographic factors such as age are associated with increased risk of HIV-SN [15, 16]. There seems to be evidence that the prevalence of the mitochondrial Haplotype T as well as the E4 isoform for Apolipoprotein E act as an independent risk factor for ATN and HIV-DSP [17, 18]. Moreover it is argued that APOE epsilon4 may play a role in nerve regeneration [18, 19].

Newer analyses demonstrate that HIV-SN also occurs increasingly with protease inhibitors as Indinavir, Saquinavir and Ritonavir [20]. However, these patients demonstrate additional

factors that are combined with an increased prevalence of polyneuropathies, such as increased age and glycometabolic disturbances. Since protease inhibitors are often applied as first-line therapies, the progressing HIV infection likewise induces an increase of polyneuropathy, which is caused by the HIV virus itself [20].

4.2 Clinical manifestation

The clinical presentation of HIV-DSP and ATN is undistinguishable and similar to other forms of DSP. Symptoms are usually length-dependent, symmetric, mainly sensory and often painful. Patients may describe burning, tightness or hyperalgesia in the feet and hands in a classic “stocking-and-glove” like pattern. Negative sensory symptoms such as numbness or hypalgesia often occur while strength is relatively preserved. Deep tendon reflexes are reduced at the ankles compared to the knees. Hyperactive reflexes may occur in cases of coexisting central nervous system disease such as myelopathy as well as HIV dementia. Significant motor involvement raises severe doubt about the diagnosis HIV-SN, although slight to moderate weakness and atrophy of the intrinsic muscles of the feet may be a feature of advanced HIV-SN.

4.3 Diagnostic evaluation

Nerve conduction studies (NCS`s) show predominantly an axonal sensory pattern with reduction of the sensory nerve action potential (SNAP) and mild reduction of the conduction velocities. As it is stated above, 20% of the patients represent exclusively with small fiber symptoms and therefore show unremarkable NCS`s [21]. One may consider conducting skin biopsy in those patients, which has been shown an objective and sensitive tool [6, 22]. Decreased ENFD was significantly associated with high plasma HIV viral levels and low CD4 counts as well as higher levels of neuropathic pain [6].

4.4 Pathogenesis

Although HIV-DSP and HIV-ATN represent identically in clinical and neurophysiological examination they have different pathogenesis.

4.4.1 HIV-DSP

The pathogenesis of HIV-DSP is incompletely understood, but is likely immune mediated. The most characteristic pathological feature is the distal degeneration of long axons [4] accompanied by macrophage infiltration [4, 23] and either the absence or modest loss of neurons in the sensory dorsal root ganglia (DRG) [24-26]. Furthermore, there is degeneration within the centrally directed extension of sensory DRG neurons [26]. These findings have led to the hypothesis that the primary pathology could be at the level of the sensory neurons in the DRG, leading secondarily to a dying back process with axonal degeneration. The diminution and degeneration of epidermal nerve fibers as seen in skin biopsies proves this hypothesis [6]. People with HIV infection have also significantly reduced rates of both collateral and regenerative sprouting in skin biopsy experimental injury models [27]. The presence of HIV-infected perivascular macrophages has been shown in the DRG of patients with and without DSP. These studies demonstrated the presence of HIV proviral DNA, mRNA, p24 antigen in these cells [28-31]. Another consistent neuropathological abnormality in the DRG appears to be the presence of activated macrophages, which express MHC antigens and pro-inflammatory cytokines [4, 29, 31]. HIV-DSP correlates with the

degree of macrophage activation [32]. Taken together, this has led to the hypothesis that activated macrophages play an important role in the pathogenesis of peripheral neuropathy. Two possible neuropathogenetic mechanisms have been proposed; the direct effect of HIV or HIV proteins such as gp120 on DRGs [33-35] and the indirect neurotoxicity of products secreted by activated macrophages [32]. The later assumption is underlined by our observation that supernatants from HIV-infected macrophages induce neuritic retraction in DRG culture, suggesting that activated macrophages may secrete neurotoxic mediators [36].

4.4.2 ATN

The increased survival time in the AIDS stage leads to a significantly higher cumulative dosage of antiretroviral agents. The toxicity of HAART is produced by a dysfunction in the mitochondria itself and mitochondrial DNA. There is evidence that the primary target in ATN is not the DRG itself but the axon [37]. Dalakas et al. described structural abnormalities in axonal mitochondria as well as mitochondria of Schwann cells in patients with ATN [38]. Mitochondrial DNA in subcutaneous fat was significantly reduced in patients currently taking Nucleoside reverse transcriptase inhibitors (NRTIs) but did however not correlate to the incidence of ATN [39].

Ddl, ddC and d4T show toxic effects on the mitochondrial DNA in tissue cultures as well. PC12 cells exposed to ddl and ddC triggered structural modifications to the mitochondria and an increase in lactate production [40]. These effects are correlated with the concentration of these substances. The initial changes to the mitochondrial ultrastructure occurred after only a few days. The toxic potential for the induction of these changes can be arranged in the following sequence: ddC > d4T > ddi [41]. The higher toxicity of ddl, ddC and d4T in comparison to other antiretroviral agents results from the diverse inhibition of mitochondrial enzymes as γ -polymerase. However there seems to be γ -polymerase independent pathways of mitochondrial damage [42].

4.5 Therapy

4.5.1 Causal

There is no approved causal treatment for HIV-associated DSP. There is however some evidence that HAART may improve symptoms [43]. Early epidemiological studies conducted during the pre HAART-era describe an annual incidence of 36% for HIV-SN compared to 21% in the HAART-era [11, 13] which also indicate some positive influence of HAART.

If the patient is taking neurotoxic medications they should be stopped or changed if it is possible. One has to check for potentially neurotoxic co medications that are often used for HIV-related conditions such as chloramphenicol, dapsone, ethambutol, etoposide, isoniazid, metronidazole, pyridoxine, thalidomide, and vincristine [44].

Clinical trials of potentially neuroregenerative therapies such as nerve growth factor [45], prosaptide [46] and timcodar [47], agents that were neurotrophic in vitro and in animal models have failed.

4.5.2 Pain management

Neuropathic pain can be quite disabling for the patients and treatment is often challenging because of concomitant diseases and relevant interactions of neuropsychopharmacologically active drugs with HAART.

Recommendations are based on studies performed specifically in HIV-SN, but also extrapolated from studies performed in various conditions such as painful diabetic neuropathy as well as postherpetic neuralgia. Six main classes of agents are used: anticonvulsants (calcium- and sodium-dependent), antidepressants, opioids, topical treatments, nonspecific analgesics and alternative therapies.

A recently published review and meta-analysis describes randomized controlled trials (RCT's) evidence of analgesic efficacy superior to placebo in the context of HIV-SN pain only for smoked cannabis, recombinant nerve growth factor (rhNGF) and high dose (8%) topical capsaicin [48]. Several other agents have been examined in RCTs and found to be not effective such as acetyl-L carnitine (1g/day), amitriptyline (100mg/day), topical capsaicin 0.075%, gabapentin (2.4g/day), mexilitine (600mg/day), peptide -T (6mg/day), pregabalin (600mg/day), lamotrigine (600mg/day) and prosaptide (16mg/day) [48, (Simpson, Schifitto et al. 2010)]. Prospective RCT's show however an effectiveness for gabapentin (up to 3.6g/d) [49] in HIV-DSP as well as lamotrigene in ATN [50].

Gabapentin and pregabalin do not induce the cytochrome P-450 system and are therefore preferred agents. Older antiepileptics such as carbamazepine should be avoided as a result of multiple and pronounced interactions [51, 52]. There are also promising data for duloxetine in reducing pain. However RCT's were performed in patients with painful diabetic neuropathy [53, 54]. Duloxetine is characterized by nearly no interactions with HAART and is therefore an interesting alternative. Even though the older, tricyclic antidepressants have not been convincing in one RCT [55] they are very well suited for neuropathic pain therapy in our clinical experience. However it has to be taken into consideration that amitriptyline levels are increased by protease inhibitors, which may provoke side effects.

5. Inflammatory demyelinating polyneuropathies

Acute inflammatory demyelinating polyneuropathy (AIDP or Guillain-Barré syndrome [GBS]) or chronic inflammatory demyelinating polyneuropathy (CIDP) may occur early in the course of HIV disease as a part of the acute antiretroviral syndrome or in a stage where the CD4 cell count is above 250/ μ l [1, 2, 56].

5.1 HIV-AIDP

In our clinical experience HIV-AIDP is a rare disease. It has not been seen in prospective studies of HIV infection [57]. A Zimbabwean study of 32 consecutive patients with AIDP found that 55% suffered from HIV, while the seroprevalence of HIV infection during the time the study took place was estimated at 4.3%, clearly indicating a relationship [2].

Cornblath et al. [1] described three patients with HIV-AIDP early in HIV infection, prior to AIDS. Subsequent reports also indicated that HIV-AIDP occurs at time of seroconversion [58, 59]. HIV-AIDP is considered to precede AIDS but has been described in HIV-infected patients with a CD4 cell count below 200 but above 50/ μ l [56, 60]. The last remark is important as one has always to consider an opportunistic polyradiculitis in patients presenting with symptoms consistent with HIV-AIDP but CD4 cells below 50/ μ l. Those patients should be treated presumptively for CMV infection until the CMV polymerase chain reaction (PCR) in CSF is negative.

The clinical manifestation is similar to those seen in HIV-negative patients with AIDP. First symptoms are distal pain, numbness, paraesthesia, or weakness in the limbs rapidly

progressing into a relatively symmetric weakness of the limbs with or without involvement of respiratory muscles or cranial nerve-innervated muscles [61]. Diagnostic evaluation for HIV-AIDP typically includes cerebrospinal fluid analysis (CSF) which might be misleading on the first glance because about 50% of the patients show mild lymphocytic pleocytosis (up to 50/ μ l) and elevated protein [62]. CSF analysis is especially important in patients with CD4 cell counts far below 200/ μ l in whom the suspicion of an underlying opportunistic or malignant etiology is high.

Treatment recommendations are derived from experiences in HIV-negative patients and include either plasmapheresis (5-7 times) or intravenous immunoglobulin (IVIg) (2g/kg/body weight) [61]. The prognosis is in general good with an almost complete remission in more than 50% of the patients [10, 56]. It seems that the relapse rate of HIV-AIDP or the development of a secondary chronic disease (CIDP) seems to occur more often [56].

5.2 HIV-CIDP

HIV-CIDP is a rare disease but in our clinical experience more common than HIV-AIDP.

Patients may present with similar clinical features like their HIV-negative counterparts but one may observe overlaps with other subtypes of HIV-associated neuropathies such as HIV-DSP or ATN which can make the diagnose challenging.

Typical clinical features include an acute or subacute onset of symptoms progressing for at least 8 weeks, a relapsing/remitting course, sometimes an asymmetrical pattern, a lack of length-dependent sensory deficits, or the presence of marked large fiber sensory deficits [63]. Sensory symptoms usually consist of numbness and tingling, but painful paresthesias may be present. Many patients have impaired balance due to proprioceptive deficits [63]. Weakness usually involves both proximal and distal muscles, but can be purely distal. Patients may reveal concomitant cranial nerve deficits [63]. As stated previously, there seems to be a higher risk for HIV-infected patients to progress from AIDP into CIDP. Those patients warrant careful consideration and follow-up as they are at risk for relapses that will require sustained treatment.

CSF analysis is usually performed, but as already mentioned shows mild lymphocytic pleocytosis (up to 50/ μ l) and elevated protein in up to 50% of the patients [62]. Diagnostic evaluation includes NCS's showing features of demyelination such as slowing of conduction velocity, prolonged distal latencies, and F-waves as well as conduction blocks and temporal dispersion [64]. Electromyography may reveal mild pathological spontaneous activity [1, 64]. A magnetic resonance image (MRI) with and without gadolinium of the corresponding spinal segments is not obligatory but is strongly recommended in patients with a CD4 cell count below 200/ μ l to exclude infiltrative processes in the nerve roots. A sural nerve biopsy is rarely necessary but may be helpful in patients representing with atypical clinical signs.

There are no RCT's in HIV-CIDP investigating treatment options. Therefore we follow the treatment recommendation for the non HIV-CIDP counterparts, where RCT's have demonstrated the efficacy of corticosteroids [65], plasma exchange [66, 67], and IVIg [68, 69]. In our view IVIGs (loading dose 2g/kg/body weight) are the best choice to start with. Corticosteroids (1mg/kg/body weight for 2-4 weeks and then tapering down or switching into an alternate-day therapy) might be another option, but one has to consider potential side effects such as immunosuppression, increased risk of osteonecrosis of the femoral head, osteoporosis and metabolic derangement. They are only a choice if the patient receives a

stable HAART. Plasma exchange is typically used if patients are severely weak or if they relapse on prednisone or IVIg [63]. Many patients require a sustained therapy but there is no general paradigm.

6. Mononeuropathy and mononeuropathy multiplex

We do see mononeuropathies with HIV-infection and they are often described in the literature [10, 22, 70]. There are however no data about the incidence. They are occurring mainly as focal cranial neuropathies such as unilateral or bilateral facial palsy [71-73]. They are described in the context of seroconversion [71] but can occur also during later stages of HIV disease. If a patient is relevantly immunosuppressed one has to consider varicella zoster virus (VZV) as well as neoplastic etiologies [72].

It is unclear whether HIV-associated mononeuropathies should prompt one to start HAART. Since we are lacking data to answer that question it cannot be recommended yet. The prognosis is in general good.

Mononeuropathy multiplex (MM) is a rare disease in HIV. Patients present often with rapidly progressive multifocal deficits and pain. The underlying etiology differs according to the stage of HIV-disease. Mononeuropathy multiplex in patients with a high CD4 count is probably immune-mediated. In contrast in patients with advanced AIDS it represents mainly an opportunistic infection like CMV-MM and shows a more severe course compared to the immune-mediated variant. Because of the high rate of co-infection with hepatitis C and secondary cryoglobulinemia it should be always considered a potential differential diagnosis.

Nerve conduction studies reveal axonal damage [74] and electromyography relevant pathological spontaneous activity in the clinically involved muscles. A CSF analysis is obligatory in patients with AIDS to search for the underlying pathology (PCR for CMV). Sural (or an alternative clinically involved nerve) biopsy is often required to show inflammatory CD8 infiltrates.

If a CMV associated mononeuropathy multiplex is suspected you may choose to treat empirically with ganciclovir and attempt HAART. The prognosis is however poor.

In patients with a high CD4 count and a suspected immune-mediated form patients may benefit from IVIg (2g/kg/body weight) or corticosteroids (100mg/d for 2 weeks, then tapering down). There are however no evidence based guidelines.

7. Autonomic neuropathy

It is not clear whether an autonomic HIV-associated neuropathy should be described as an isolated entity because according to our knowledge it is not known, that patients present with purely autonomic symptoms [10]. Autonomic symptoms however are often in other HIV-neuropathies, for instance HIV-SN. Studies investigating autonomic functions in HIV-infected patients describe different in part contrary results [75-79], which urges the need for larger RCT's.

8. Diffuse infiltrative lymphocytosis syndrome (DILS)

DILS is a very rare systemic disease involving several organs including the peripheral nervous system. To our knowledge it occurs exclusively in HIV-infected patients [80, 81]

during the middle or advanced stages of HIV disease while the CD4 cells are below 500/ μ l. The most common manifestations are bilateral parotid enlargement, pulmonary insufficiency, and lymphadenopathy [81]. Neurological manifestations of DILS include peripheral neuropathy, which can be the presenting symptom [82]. It has been described as a painful, symmetric neuropathy with acute or subacute onset. Other neurological manifestations are facial nerve palsy (uni- or bilateral) as well as myositis [83]. Recently a lumbosacral radiculoplexus neuropathy has been described as a clinical presentation of DILS [84].

The typical syndrome includes CD8-lymphomatosis (>1200/ μ l) and secondary infiltration of the visceral organ and peripheral nerves [81, 82, 85-87]. Sural nerve biopsy reveals epi- and endoneural infiltration by CD8 cells and vascular mural necrosis [82, 85]. Increased expression of HIV p24 has been demonstrated in macrophages infiltrating the nerves [80, 82, 88].

DILS is a rare disease so there are no RCT's for treatment regimens. It is described, that patients show improvement with corticosteroids and zidovudine [82]. It is therefore recommended to initiate or continue HAART and start with corticosteroids (1 mg/kg body weight for 4 weeks then tapering slowly down to 10-20 mg) [70].

9. Radiculopathies

Progressive polyradiculopathy is seen in patients with advanced AIDS [89]. They are mainly CMV-associated but can be also caused by *Treponema pallidum*, VZV, EBV, HSV, mycobacterium tuberculosis or cryptococcus neoformans [62, 90-92]. Patients present with a rapidly evolving cauda equina syndrome, including weakness and numbness in the lower extremities and sphincter dysfunction [90].

Mandatory diagnostic evaluation includes an MRI of the lumbosacral spine, which may show meningeal enhancement [93] as well as CSF analysis. A spinal tap is essential to confirm the underlying opportunistic infection in the CSF (PCR) as well as malignancy (cytology). CSF can be surprisingly unremarkable which would still not exclude the diagnosis [94] because of the severe immunosuppression. Nerve conduction studies reveal severe axonal damage in the lower extremities combined with extensive pathological spontaneous activity in the electromyography. If a CMV infection is suspected it would speed up the diagnose to search for evidence of CMV infection in other organs (retinitis, pneumonitis, hepatitis) [10, 22].

Treatment follows the underlying etiology [95]. In cases of CMV - polyradiculitis ganciclovir is effective or alternative foscarnet, and cidofovir [89, 96, 97].

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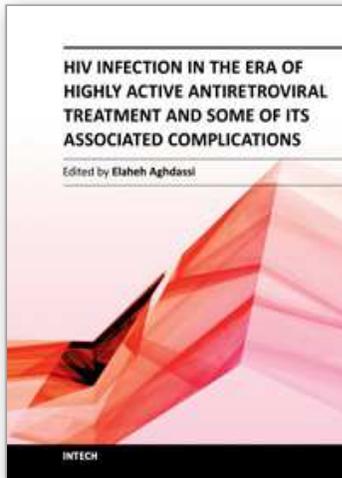
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HIV Infection in the Era of Highly Active Antiretroviral Treatment and Some of Its Associated Complications

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Human immunodeficiency virus (HIV) infection is a complex illness affecting the immune system. Acquired immunodeficiency syndrome (AIDS) is an advanced form of HIV infection in which the patient has developed opportunistic infections or certain types of cancer and/or the CD4+ T cell count has dropped below 200/ μ L. More than 40 million persons around the world are infected with HIV, with approximately 14,000 new infections every day. The disease causes 3 million deaths worldwide each year, 95% of them in developing countries. Optimal management of human immunodeficiency virus requires strict adherence to highly active antiretroviral treatment (HAART) regimens, but the complexity of these regimens (e.g., pill burden, food requirements, drug interactions, and severe adverse effects) limits effective treatment. However, more patients with HIV are surviving longer today because of these drugs. This allows further study of commonly associated adverse effects. These may affect all body systems and range from serious toxicities to uncomfortable but manageable events. This book reviews some of HAART-related metabolic and neurological complications.

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