PERIPHERAL NERVE DISEASE IN HIV-INFECTED SUBJECTS

AN AFRICAN PERSPECTIVE

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Overview

- Epidemiology
- Classification
- Pathology and neurophysiology
- Clinical characteristics
- Investigations
- (Management)
- (Prognosis)
Classification

- Distal Symmetrical polyneuropathy (DSP)
  - Idiopathic
  - Associated with neurotoxic drugs
  - Associated with vitamin B\textsubscript{12} deficiency
- Inflammatory demyelinating polyneuropathy
- Mononeuropathy (multiplex)
- Progressive polyradiculopathy
- Autonomic neuropathy
<table>
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<tr>
<th>HIV-associated PNS disorder</th>
<th>CDC stage</th>
<th>Course</th>
<th>Clinical features</th>
<th>Mechanism</th>
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<td><strong>Distal sensory neuropathies</strong></td>
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<tr>
<td>Distal symmetrical polyneuropathy</td>
<td>AIDS, CDC C</td>
<td>Subacute or chronic</td>
<td>Distal sensory loss, neuropathic pain</td>
<td>Immune dysfunction, ? Macrophage-mediated axonal injury</td>
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<tr>
<td>Antiretroviral toxic neuropathy</td>
<td>Any stage, CDC A-C</td>
<td>Subacute</td>
<td>Distal sensory loss, neuropathic pain</td>
<td>? DRG neuronal mitochondrial dysfunction</td>
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<td><strong>Mononeuritis multiplex</strong></td>
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<td>Vasculitic neuropathy</td>
<td>Symptomatic HIV disease, CDC B</td>
<td>Stepwise progression</td>
<td>Multiple, asymmetric mononeuropathies, usually painful</td>
<td>Dysimmune/vasculitic mechanisms</td>
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<td><strong>Mononeuritis multiplex due to opportunistic pathogens</strong></td>
<td>AIDS, CDC C</td>
<td>Acute, subacute</td>
<td>Multiple, asymmetric mononeuropathies, usually painful</td>
<td>CMV infection, VZV infection, hepatitis B and C (especially with cryoglobulinemia)</td>
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<td><strong>Inflammatory demyelinating polyradiculoneuropathies</strong></td>
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<td>Acute inflammatory demyelinating polyradiculoneuropathy</td>
<td>Early, pre-AIDS</td>
<td>Acute</td>
<td>Motor to sensory signs, NCS reveal demyelinating features</td>
<td>Immune dysfunction: macrophage/complement mediated demyelinating neuropathy</td>
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<td>Chronic inflammatory demyelinating neuropathy</td>
<td>Early, pre-AIDS</td>
<td>Subacute to chronic</td>
<td>Sensorimotor neuropathy, NCS show demyelinating features</td>
<td>Immune dysfunction</td>
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<td><strong>Progressive polyradiculopathy</strong></td>
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<td>CMV polyradiculopathy</td>
<td>AIDS</td>
<td>Acute</td>
<td>Lumbosacral pain, saddle anesthesia, rapidly progressive flaccid paraparesis</td>
<td>CMV infection, necrotizing neuropathy</td>
</tr>
<tr>
<td>Herpes zoster radiculopathy or myeloradiculoathy</td>
<td>AIDS</td>
<td>Acute</td>
<td>Lumbosacral pain, saddle anesthesia, rapidly progressive flaccid paraparesis</td>
<td>VZV infection: Schwann cell and endothelial cell infection</td>
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Epidemiology: USA

- Of 187 patients, 99 (53%) had DSP. (Simpson et al 2004)
- Patients with neuropathy were older than those without (45.3 vs 41.2 years)
- DSP was significantly more common in men (58%) than in women (37%)
- The presence of neuropathy was not correlated with plasma viral load, decreased CD4 cell counts, or neurotoxic antiretroviral therapy.
- Twenty-six of 99 patients with DSP were asymptomatic.
- Asymptomatic neuropathy was correlated with histories of opiate and sedative abuse and dependence.
- Symptomatic DSP correlated with ethanol and hallucinogen syndromes, but not neurotoxic therapy.
- In contrast to populations before the era of highly active antiretroviral therapy, DSP is **not associated** with increased viral load or decreased CD4 cell counts in this cross-sectional analysis. Symptoms in DSP **are associated** with substance use disorders.
Peripheral neuropathy in Uganda

- Wong et al – 2004 (81 HIV-positive)
- Symptoms in 37%
- Signs of sensory neuropathy in 46% of HIV+
- Questions about the use of d4T (stavudine) in first-line treatment in resource-limited settings. Peripheral neuropathy caused by HIV disease is worsened by d4T and by the combination of d4T and ddl
Peripheral neuropathy in Burkina Faso (Millago et al, 2002)

- 46 cases (presenting with peripheral neuropathy and HIV+)
- Facial nerve palsy in 25 patients - 15 women,
- Average age 34 years.
- 80% CD4 count > 200
- 5/10 cases of polyneuropathy occurred at early stage of HIV infection.
- Herpes zoster occurred early in 5/7 cases.
- 3/4 cases of polyradiculopathy CD4 count < 200
Peripheral neuropathy in Harare

- 120 subjects: 33 controls, 35 asymptomatic, 23 symptomatic, 30 AIDS (defining)

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<tr>
<th>Type</th>
<th>Asymptomatic</th>
<th>Symptomatic</th>
<th>AIDS (%)</th>
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<tbody>
<tr>
<td>Sub-clinical</td>
<td>17</td>
<td>35</td>
<td>37</td>
</tr>
<tr>
<td>DSP</td>
<td>0</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>0</td>
<td>0</td>
<td>2</td>
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</table>
Distal Symmetrical polyneuropathy

- First described 1983 (Snider et al, Simpson)
- Clinical and electrophysiological signs in >\(\frac{1}{3}\) of AIDS victims
- Pathological evidence in almost all AIDS victims dying.
Pathology

- Axonal degeneration, myelinated and unmyelinated
- Some demyelination (non-segmental, not macrophage-mediated)
- T lymphocytes and activated macrophages perivascular, endoneural and epineural
- Suppressor / cytotoxic cells predominate
- Less cell body and central tract loss
(a) Skin biopsy from control   (b) HIV patient with DSP

Note the decreased number of epidermal nerve fibers and formation of nerve fiber swellings
Pathogenesis

- Speculations:
- Indirect:
  - Activated macrophages and proinflammatory cytokines enter dorsal root ganglia and peripheral nerves via leaky blood-nerve barrier → more chemokine and cytokine release
  - Excessive macrophages in Wallerian degeneration, i.e. nutritional deficiencies, alcohol, substance abuse result in greater axonal degeneration
- Direct HIV infection
  - Viral proteins (gp 120) toxic to dorsal root ganglia neurons → dying back axonal degeneration
Clinical features

- **Symptoms**
  - **Presenting:**
    - Burning feet (⅔)
    - Parasthesiae (⅓)
  - **Incidental diagnosis:** (13 / 40 in one series)
    - Numbness (⅓)
    - Parasthesiae (⅓)
    - Pain or discomfort (¼)
  - Symmetrical sensory symptoms, weakness very late
Clinical features

- **Signs:**
  - Depressed or absent ankle jerks in all
  - Elevated vibration threshold in feet (85%+)
  - Pain and temperature threshold commonly ↑
  - Joint position sense usually normal
  - Minor toe weakness / mild intrinsic foot wasting
  - Hands very late
  - Almost all have AIDS
Electrodiagnosis

- Mean sural nerve conduction velocity significantly reduced in asymptomatic HIV+
- Small or absent sural sensory nerve action potentials (SNAPs) in DSP
- Sensory and motor nerve velocity much less affected than amplitudes
- EMG may demonstrate partial denervation/reinnervation in distal leg muscles
- Summary: distal symmetrical axonal degeneration
DSP with neurotoxin exposure

- NRTIs: zalcitabine (ddC), stavudine (d4T) and didanosine (ddl).
- Onset 1 week to 6 months, depending on the NRTI and the dose. The onset is typically more acute than the onset of DSP, and pain may be more prominent.
- Symptomatic improvement weeks to months in about two-thirds of patients after discontinuation, often preceded by an initial period of worsening symptoms.
- In many cases, these two conditions are indistinguishable. The failure of at least one-third of cases of TNA to improve upon cessation of the precipitating NRTI increases the difficulty of distinguishing TNA from DSP.
- Vincristine
- Isoniazid
Incidence rates of TNA/100 person years in 1116 patients, receiving one of five antiretroviral regimens and followed by the Johns Hopkins AIDS Service.
DSP and $B_{12}$ deficiency

- 16% of HIV infected for neurologic evaluation
- 30% of DSP (and $\frac{2}{3}$ of DSP and myelopathy) had $B_{12}$ abnormalities
- 5 of 8 treated had improvement of symptoms one week after $B_{12}$ treatment
Inflammatory Demyelinating Polyneuropathy

- Guillain Barre syndrome (AIDP) and chronic inflammatory demyelinating polyneuropathy (CIDP)
  - GBS: acutely (up to four weeks) progressive generalised weakness with areflexia and mild sensory impairment
  - CIDP: longer course, monophasic or relapsing
  - Often seen in asymptomatic HIV+
Inflammatory Demyelinating Polyneuropathy

- Electrophysiological features of segmental demyelination, often proximal:
  - Slowing of conduction velocity
  - Conduction block
  - Absent or prolonged F waves

- CSF: raised or rising protein, +/- pleocytosis

- Treatment as for HIV-: immune therapies
Multiple Mononeuropathy

- Multifocal sensory complaints in the distribution of cutaneous nerves, mixed nerves and roots.
- Asymmetrical distribution, preserved reflexes
- Two syndromes: “limited” in those with CD$_4$ >200, “extensive” in others with concomitant CMV infection
- Nerve biopsy often necessary (immune suppression vs specific Rx e.g. ganciclovir)
Progressive Polyradiculopathy

- Frequent CMV association (also VZV infection, neurosyphilis and leptomeningeal lymphoma)
- Rapid progression –
  - Lower extremity and sacral parasthesiae
  - Paraparesis, areflexia, ascending sensory loss (occasional thoracic level) and urinary retention
  - Cauda equina pain
  - Onset to deaths - six weeks
- CSF: WBC ↑ (polymorphs), protein ↑, glucose ↓