HIV and chemotherapy induced neuropathy

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IMMPACT 2009

Major Neuromuscular Syndromes in HIV Disease

Diagnosis and HIV stage

Sensory neuropathies (DSP, ATN): Variable
Mononeuropathy multiplex: Early (limited); Late (progressive), Hep C
Distal sensory polyneuropathy DSP
Antiretroviral toxic neuropathy ATN
Progressive polyradiculopathy: Late, CMV
Inflammatory demyelinating polyneuropathy: Early
Myopathy: Any (AZT); Early (polymyositis); IBM
ALS-type disorder: Late, rare
HIV-associated neuromuscular weakness syndrome: D4T

Confounding illnesses in the assessment of HIV sensory neuropathies

- Antiretroviral exposure: d4T 8-fold, ddI 4-fold
- Diabetes in 11% of HAART recipients; IGT in ~ 20%
- Alcohol abuse; hepatitis C
- Entrapment neuropathies
- Vitamin deficiencies or overuse
- Morton’s neuroma

HOPS: declining incidence of neuropathy

Lichtenstein CID 2005

Incidence rates of 15 AIDS-defining events in 5 time periods after initiation of highly active antiretroviral therapy (HAART)

- CHARTER is a multicenter, observational, NIH contract study designed to assemble a cohort that is similar to the clinic population
  - Overall objective: Determine the effects of antiretroviral therapy on the nervous system
- Study procedures include
  - Comprehensive neuropsychological and neuromedical assessments
  - Phlebotomy and lumbar puncture
  - Neuroimaging
  - Specialized neuropathy assessments

CHARTER
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Pathogenesis of sensory neuropathies in HIV/AIDS: summary

- Epidermal denervation and prominent DRG macrophage activation;
- Denervation of Schwann cells and mitochondrial abnormalities (Ebenezer et al. 2007)
- Some NRTIs are toxic to DRG cultures (Ebenezer et al. 2007, Hoke et al. 2005, Zhu, 2008)
- gp120 causes a dose-dependent axonal degeneration in sensory neurons in DRG cultures, mediated by apoptosis (Hoke, 2005)

Antiretroviral toxicity

Macrophage activation and neuronal reduction in DRG correlates with HIV-SN

Distribution of pain in ALLRT cohort

Evans S. CROI 2009

Frequency of neuropathic signs: CHARTER cohort

From Ronald J. Ellis, CROI 2009

Distribution of pain in ALLRT cohort

Evans S. CROI 2009

ACTG

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Antiretroviral toxicity

Stavudine

Distribution of pain in ALLRT cohort

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Pathogenesis of sensory neuropathies in HIV/AIDS: summary

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- gp120 causes a dose-dependent axonal degeneration in sensory neurons in DRG cultures, mediated by apoptosis (Hoke, 2005)
Increasing height was associated with toxic neuropathy risk. A model including cytokine genotype and height predicted NRTI-SN status (p < 0.0001, r² = 0.54).

Late onset NRTI-SN patients clustered genetically with NRTI-SN-resistant patients, so these patients may be genetically "protected." Cytokine genotype influenced SN risk following dNRTI exposure, suggesting that inflammation contributes to NRTI-SN.

**Skin biopsy: use in clinical diagnosis of sensory neuropathy**

- Utility of skin biopsy:
  - selective for small caliber nerve fibers and can distinguish neuropathy from radiculopathy from psychogenic
  - standardization and QC among 10 CLIA-approved labs
  - now accepted as validated outcome measure in clinical trials and for the diagnosis of SFSN

**AAN practice parameters**

*Neurology 2009;72:1–1*

- "IENF density assessment using PGP 9.5 immunohistochemistry is a validated, reproducible marker of small fiber sensory pathology. Skin biopsy with IENF density assessment is possibly useful to identify DSP which includes SFSN in symptomatic patients with suspected polyneuropathy (Class III)."

**HIV sensory neuropathies**

Skin biopsy assesses unmyelinated nerve fibers

Thigh: normal density        Distal leg: reduced density and nerve fiber swellings

**Skin biopsy technique**

Fresh punch sites

3mm punch

Healed scar ~ 2 weeks

**Morphological abnormalities on skin biopsies**

Segmented dermal fibers

Nerve fiber swellings
Correlates of epidermal nerve fiber densities in HIV-associated distal sensory polyneuropathy

Table 1: Total Neuropathy Score (TNS) scores and distal epidermal nerve fiber density

<table>
<thead>
<tr>
<th>Symptom Measure</th>
<th>Total Neuropathy Score (TNS)</th>
<th>Distal EPI Nerve Fiber Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>13.0 ± 1.4</td>
<td>20.0 ± 2.2</td>
</tr>
<tr>
<td>Yes</td>
<td>13.0 ± 1.4</td>
<td>20.0 ± 2.2</td>
</tr>
<tr>
<td>TNS</td>
<td>8.5 ± 0.5</td>
<td>15.5 ± 1.0</td>
</tr>
<tr>
<td>Total</td>
<td>10.0 ± 0.5</td>
<td>18.0 ± 0.5</td>
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</tbody>
</table>

Distal calf intraepidermal nerve fiber density (IENFD) measurements by clinical neuropathy and symptom status

Developing models to study nerve injury in HIV-associated sensory neuropathies...

- Punch skin biopsy assessment of epidermal nerve fibers and SCs
- Capsaicin denervation and regenerative regrowth
- Intracutaneous axotomy and collateral sprouting
- Sural nerve biopsy

Mechanisms of nerve fiber repair after cutaneous nerve injury

- Regenerative regrowth ~ from transected nerve fibers along denervated Schwann cell bands
- Collateral sprouting from uninjured nerve fibers in neighboring skin

A healthy Remak bundle at the papillary dermis containing 3 axons surrounded by collagen. (x25K)

Healthy control

HIV neuropathy
SIV macaque model of HIV DSP
(Mankowski J, Laast V, Zink MC, Clements J)

Epidermal nerve fiber density (% volume immunopositive for nerve fiber marker PGP 9.5) decreases with severity of DRG ganglionitis.

CD68 immunostaining for activated/infiltrating macrophages in DRG of SIV-infected macaques showing significant increase in macrophage staining in DRG.

Excision model to study regeneration in human cutaneous nerve injury: collateral sprouting

Rajan B., 2003

SIV infection alters epidermal nerve fiber length post-axotomy
(Ebenezer G., 2009)

Shorter sprout length at earlier time points (lower mean ratios of collateral sprout length (S) to normal nerve fiber length (N)) indicating altered kinetics of regeneration.

Nerve fiber repair is as impaired in HIV infection as in diabetes

Agent | Outcome | Comments
---|---|---
Amitriptyline v. acupuncture | No effect | sham acupuncture used
Topical agents | Lidocaine No | advantage of intermittent topical therapies compared to oral agents
Amitriptyline v. meptilene | No effect | underpowered
Gabapentin | Pain improved | n = 26
Duloxetine | Pain improved | no effects over 48 weeks on ENF
Lamotrigine | Pain improved | 2 separate trials differential placebo effect in ATN
High-Concentration Capsaicin Patch (NGX-4010)

**Application Procedure**

![Application Procedure Image]

C107: Time Course of Pain Change with T NGX-4010/Qutenza®

**Percentage Change from Baseline at Weeks 2-12**

![Time Course Graph]

Potential issues with high dose capsaicin strategy

- Potential dangers of deafferentation
- Does regrowth of fibers occur, with increased excitability?
- The most common adverse reactions associated were redness, pain, and itching at the application site.

Has the potential for periodic treatment of painful neuropathies without need for continued exposure to agent

Chemotherapy neuropathy: Measuring inches with a yard stick

**Table 1. Comparison of Classification Systems for Multifocal Sensory Neurotoxicity**

<table>
<thead>
<tr>
<th>Code</th>
<th>NCI-CTC</th>
<th>CTS Specific Term</th>
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<tbody>
<tr>
<td>S</td>
<td>Loss of deep tactile sensation or numbness including vibration but not parasthesias or pain</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Objective loss of vibration including tingling, scratching, perniosis, or pain</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>Sensory loss or paresthesias without evidence of deep-lingual function</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Persistent sensory loss due to other risk factors</td>
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</tbody>
</table>

Abbreviations: NCI-CTC, National Cancer Institute Common Terminology Criteria for Adverse Events

Ixabepilone—approved despite neurotoxicity

NCI-CTC vs TNS: which tool is better for grading the severity of chemotherapy-induced peripheral neuropathy?

- The TNS and the TNSc were significantly correlated with the NCI-CTC in scoring CIPN severity.
- All patients with a 1-point change on the NCI-CTC scale had a 2-point difference in the TNS (84% with a change of ≥ 2 points).
- “As a research tool for measuring change in clinical trials and as a clinical tool for following change during neurotoxic drug treatment, the TNS and TNSc are clearly an advance on what has gone before.”

Predictors of CIPN

- Baseline neuropathy
- Co-morbid conditions (DM)
- Age
- Variation
  - Pharmacogenetics
  - Tumor type (Bortezomib)
• chemotherapy-induced peripheral neuropathy outcome measures standardization study (CI-Perinoms) where impairment, disability, quality of life, and patient-reported outcome measures will be formally compared using a clinimetric approach—

Epidermal Innervation holds promise

Study Outline: Oxaliplatin toxicity
• Visit 1 (Baseline) prior to starting oxaliplatin
• Visit 2 (1 month)
• Visit 3 (3 months)
• Visit 4 (6 months)—completion of therapy
• Visit 5 (Follow-up, 12 months)—6 months after completion

Hypotheses
• Baseline nerve fiber density would predict development of neuropathy
• Older patients would develop more severe CIPN
• Patients with co-morbidities (DM) would have more severe CIPN
• Improvement between 6 and 12 months.
• CIPN would be predominantly SFSN

Sural Amplitude

Epidermal Innervation

Skin biopsy: a window into peripheral nerve morphology
Advantages of epidermal innervation

- Truly blinded
- Relatively non-invasive, safe
- Ability to re-sample

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