Case Presentation

- 66 man presents with 2 year history of progressive numbness, tingling, and burning paresthesias
- Symptoms primarily in feet up to shins, more recently in hands
- No history of DM, EtOH or chemical exposures. No FH of neuropathy
- Examination:
  - Decreased sensation to PP/LT in feet up to shins, and in distal fingers
  - Absent vibration and reduced proprioception in ankles and toes
Polyneuropathy (PN)

• Epidemiology
  – Incidence 25-200 per 100,000 persons/year (MacDonald et al, 2000; IGPSG 1995)
  – Prevalence up to 5% (ILSAWG, 1997)

• Classification by Fiber type involvement
  – Large fiber: sensory/motor
  – Small sensory fiber: autonomic, somatic

Laboratory Studies:

• Oral GTT - 60% presumed cryptogenic PN found to have DM or impaired glucose with OGTT (Homan-Snyder et al, 2006)

• Complete metabolic profile: EtOH, renal disease

• B12
  – Etiology in 2-8% of PN patients (Mygland, 2007)
  – Prevalence of B12 deficiency in up to 14.5% in elderly
  – MMA and homocysteine with B12 <300 (up to 600)
  – Also check CBC for macrocytic anemia
Laboratory Studies:

- SPEP or Immunoelectrophoresis
  - M protein positive in 10% idiopathic PN patients (Nobile-Orazio, 2004)
  - In contrast, 2.5% of PN patients with known cause have MGUS (Kelly et al, 1981)
  - 10% monoclonal gammopathy patients have underlying malignancy (Eurelings et al, 2005)
  - Further workup may be needed if abnormal: skeletal survey, urine protein analysis, bone marrow, VEGF

- Thyroid function testing: TSH, T4

- Inflammatory/Vasculitis screening: ANA, CRP, ESR, RF, SSA/B, ACE

Antibody Testing

- Most autoAb testing do NOT define specific clinical syndrome or play a pathologic role (Vernino 2007)
  - Anti-sulfatide Ab
  - Predicted frequency only 0.7% in idiopathic PN (Lopate et al, 1997)
  - Distal sensory axon loss PN, pain, ataxia
  - Low positive titers in asymptomatic pts, HIV, hepatitis, ITP

- Paraneoplastic Ab
  - Sensory neuronopathy and sensorimotor PN (anti-Hu)
  - More rapidly progressive clinical course
  - CA risk factors (tobacco) and signs (weight loss)
Antibody Testing

- Celiac disease
  - GI (diarrhea and weight loss), dermatitis herpetiformis rash
  - Mild sensory axon loss PN common, although some reports only 8% (Chin, 2003; Mygland 2007)
  - Tissue transglutaminase Ab, antigliadin IgA, IgA antiendomysial Ab for screening, but small bowel biopsy necessary for definitive diagnosis
Genetic testing – Axon Loss PN

• CMT2

• Fabry’s disease:
  – alpha galactosidase A activity
  – Suspect in young men and intense burning paresthesias in hands and feet

• Tangier’s disease
  – Remitting asymmetric sensory predominant PN
  – Bi-brachial neuropathy
  – Low HDL

CSF analysis

• Low yield in distal symmetric axon loss PN
• More helpful for demyelinating disease
• Diagnosis driven
• Malignancy: cytology and flow cytometry
• Infection: HSV, CMV, Lyme
• IgG indices (Tourtellotte’s)
• ACE (30% sensitivity)
Nerve Biopsy

• Main indication: vasculitic neuropathy

• Also helpful for sarcoidosis, infection (leprosy, CMV) neoplastic disease (lymphoma, amyloid)

• Biopsy results led to diagnosis in 14-37% pts with cryptogenic PN, but resulted in therapy for only 19% Complications: (47 patients after mean f/u 24 months)
  – 30% chronic pain sural nerve distribution
  – 47% dysesthesias
  – 72% persistent sensory loss
  – Only 51% would submit to biopsy again

Skin Biopsy

• Minimally invasive

• 3mm diameter punch biopsy ankle, distal thigh, proximal thigh

• Immunostained with PGP 9.5 panaxonal marker

• Reduced Intraepithelial nerve fiber density (IEFD)

• 88% sensitive (Low et al, 2006; McArthur et al 1998)
Skin Biopsy

Normal skin biopsy

**QSART**

- Measures sweat output in response to acetylcholine iontophoresis
- Reflects function of postganglionic sympathetic unmyelinated sudomotor fibers
- Output and latency compared to normative values
- 72% sensitivity (Novak et al, 2001)
Back to the Case

- Free monoclonal kappa light chains in the urine
- ESR, CRP, monoclonal protein serum, B12, homocysteine, MMA, ANA, oral GTT, TSH, CMP, CBC all normal
- Repeat urine monoclonal protein analysis 2 weeks later negative
- Followup 2 years later: marked worsening of sensorimotor deficits, now with severe gait ataxia, LE weakness up to and involving the hip flexors
- Repeat labs and urine monoclonal protein analysis negative, but creatinine now 3 and BNP 1933 (nl<125)
Diagnostic Evaluation - Summary

- Laboratory studies
  - Routine chemistries
  - Antibody testing
  - Genetic panel
- CSF
- Nerve biopsy
- Small fiber testing
  - QSART
  - Skin biopsy: intraepidermal nerve fiber density
REFERENCES