

Peripheral Neuropathy Update

Hawaii Association of Osteopathic Physicians and Surgeons
Conference

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I have nothing to disclose.

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Objectives

- Describe symptoms
- Describe anatomy
- Discuss diagnosis
- Plan treatment

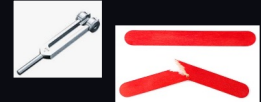


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Neuropathy: clinical symptoms

Sensory:

- Numbness
- Paresthesias, hyperalgesia, allodynia
- Large fiber – vibration, proprioception
- Small fiber – pain / temperature



Motor:

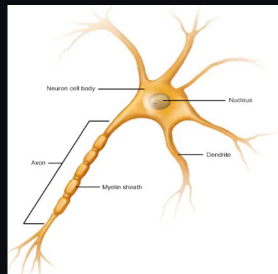
- Weakness, atrophy
- Loss of reflexes

Autonomic: Orthostasis, impotence, gastroparesis, constipation

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Anatomy

- Clinical symptoms
- Onset / pace of progression
- Anatomic Distribution
- Modality involved



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Neuropathy: etiology

Metabolic – **Diabetes**,
Uremic, Thyroid
Nutritional – **B12, B1, B6**
Toxic – **alcohol**, lead,
chemotherapy, agent
orange
Inflammatory – CIDP,
vasculitis, paraneoplastic

Infectious – HIV, leprosy,
Lyme's
Paraproteinemic – MM,
MGUS
Rheumatologic – SLE,
Sjogren's, RA
Genetic
Idiopathic

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Neuropathy: onset and pace

Onset and pace of progression

Chronic onset with slow progression

– **toxic / metabolic**

DM, B12 deficiency, EtOH, HIV,
hereditary, idiopathic

Acute / Subacute – **inflammatory**

GBS, CIDP, paraproteinemic, hep
C, rheumatologic, chemo

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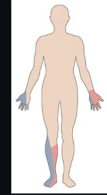
Neuropathy: Distribution



Length-
dependent,
symmetric



Proximal
/ distal



Multifocal

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Neuropathy: Modality

Sensory involvement early with
late / mild motor involvement -

Toxic / metabolic

DM, B12 deficiency, chemo,
EtOH, HIV, hereditary,
idiopathic

Large fiber vs small fiber vs
both

Motor involvement early with
sensory loss - **Inflammatory**

GBS, CIDP, Paraproteinemic

Prominent proprioceptive loss

Sensory neuronopathies (Hu
/ CRMP5, SSA), dorsal
column

Pure motor

MMN, MND, (myopathy,
myasthenia)

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Neuropathy: broadly

Typical Neuropathy:

Gradual progression over years: distal, sensory predominant, axonal

Red flags:

Subacute progression; greater than expected motor involvement;
weakness in a mononeuropathies multiplex OR proximal + distal
pattern; extensive pure sensory loss

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Neuropathy DX: Lab work

First Line:

CBC, basic metabolic
panel, LFTs

HbA1c

Vitamin B12

SPEP

TSH

Second Line:

ANA, SSA / B, RF, ESR, ANCA

Vitamin B1, B6

HIV

Hepatitis B and C

Cryoglobulin

Celiac testing

UPEP with IFE

Paraneoplastic panel-send out

Genetic testing

Heavy metal

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Nerve conduction study / EMG

NCS

Stimulate a nerve with electricity and monitor

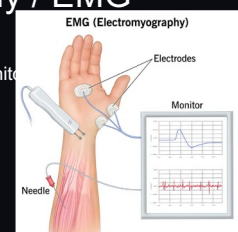
Large-fiber sensory and motor nerves

Axonal vs demyelinating

EMG

Insert a needle into muscles and listen

Muscles at rest and during activation



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Abnormal SPEP?

An M spike is associated with peripheral neuropathy.

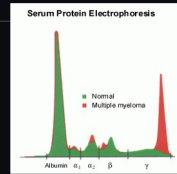
Abnormal SPEP?

-Order IFE

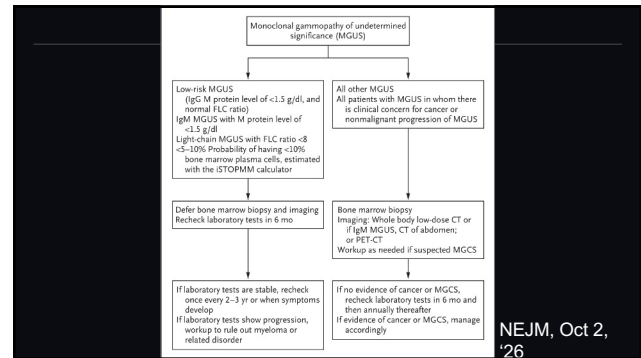
-Serum free light chain assay

-UPEP

-Ca



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Skin / nerve biopsy

Skin punch

Evaluation of small fiber neuropathy

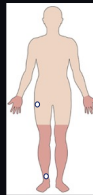
80% sensitivity, can solidify diagnosis but not etiology

Nerve Biopsy (Sural Nerve)

Subacute progressive neuropathy

Causes a permanent neurologic deficit

Evaluates for vasculitis, neurolymphomatosis, amyloid, sarcoid



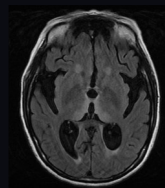
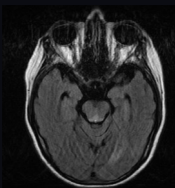
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Case 1:

35yo M w/ a 2-wk hx of ascending lower limb weakness and painful hand + foot paresthesiae. Working dx was Guillain-Barré. Soon after admn, he became confused with deficits in MS including recall and difficulty w/ commands. CN exam = bilateral impaired ocular abduction. He had mild, bilateral, proximal, + distal limb weakness. He had graduated impairment of PP and LT to knees + wrists. Reflexes were absent. Mild appendicular dysmetria + severe gait ataxia were present. Brain MRI = T2-signal in periaqueductal gray + medial thalami. LP was unremarkable. NCV + EMG = axonal neuropathy w/ acute denervation. It was subsequently discovered that during the preceding 2 mos he was drinking 4 -5 glasses of wine/d, had a 15-pound weight loss, and his po intake was limited.

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Case 1:



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Nutritional Neuropathies

Deficiencies in B-vitamins (B1, B3, B6, B12), Vitamin E, Copper

Especially with malnutrition, alcohol abuse, gastric bypass;
Low threshold to send labs

Management: repletion (look up the dose)

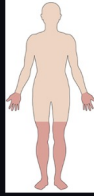
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Nutritional Neuropathies

Onset / Pace: Gradual / progressive course
Though may also present sub-acutely

Distribution: Distal length dependent

Modality: sensory > motor deficits



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Case 1: Thiamine Deficiency

Dietary sources

Whole grains, fortified grains, fish, meat

Deficiency causes

Increased requirement: pregnancy, children, critical illness, malignancy

Malnourishment: alcohol, anorexia, vomiting, starvation, bariatric surgery, GI disease

Symptoms

Wernicke encephalopathy, Korsakoff psychosis, GBS-like presentation, neuropathy

Lab: whole blood thiamine

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Vitamin B12 Deficiency

Dietary sources

Meat, poultry, fish, eggs, dairy products

Deficiency causes

Pernicious anemia, advanced age, vegan

/ vegetarian diet, alcohol, bariatric surgery, NO toxicity

Symptoms

Neuropathy, myelopathy, neuropsychiatric symptoms, optic neuropathy, anemia

Lab

B12, MMA, homocysteine;

May take years to deplete body B12 stores

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Vitamin B9 (Folate) Deficiency

Dietary Sources

Vegetables, fruits, beans, nuts, eggs, milk, meats, seafood, fortified grains

Deficiency Causes

Alcohol, GI disease, folate antagonist (**methotrexate**)

Symptoms

Mirrors B12 deficiency

Lab

Serum folate, RBC folate, homocysteine

Cooking destroys folate in foods; folate deficiency often takes 2-3 months

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Vitamin B3 (Niacin) Deficiency

Dietary sources:

Meat, poultry, fish, mushrooms, nuts, legumes, grains, eggs, grains

Deficiency causes:

Corn as primary carbohydrate, alcohol, carcinoid, B6 deficiency, dialysis

Encephalopathy, neuropathy,

Lab:

Urinary excretion of metabolites (not very reliable)

Consider in Wernicke's that does not respond to thiamine

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Dermatitis of Hands, "Casal's Necklace"



From MD Search light

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Vitamin E

Dietary sources:

Vegetable oils, leafy vegetables, whole grains, nuts

Deficiency causes:

Liver or pancreatic disease

Symptoms

Neuropathy, myelopathy, ataxia

Lab

Serum vitamin E

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Copper

Dietary sources:

Shellfish, nuts, seeds, whole grains, beans, chocolate

Deficiency causes:

GI surgery, zinc toxicity, enteral nutrition, celiac

Symptoms

Myelopathy, neuropathy, optic neuropathy

Oral iron may interfere with copper absorption

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Case 2

A 20 yo M presented with gait disturbance. He reported a normal developmental history except for difficulty running like other children and frequent ankle spraining in adolescence. As he got older, he noticed numbness in toes and developed significant foot deformity and imbalance. His FH revealed similar symptoms in his brother and father. He had distinct foot morphology in the form of high arches and hammer toes. Strength was 4/5 for finger abduction, ankle dorsiflexion, and foot eversion. Reflexes were unobtainable. He had gradient sensory loss to pinprick at the midfoot, and vib loss. He had a prominent steppage gait. His NCV showed slowing of motor conduction velocities.

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Case 2

Motor nerve and sites	Distance, cm	Latency, ms	Amplitude, mV	Velocity, m/s
Right median, abductor pollicis brevis				
Wrist	6	13.1	6.3	
Elbow	22.5	25.7	5.8	17.8
Right ulnar, abductor digiti minimi				
Wrist	6	8.5	5.6	
Below elbow	19.5	19.4	5.3	17.8
Above fibular	10	23.4	5.0	18.4
Right peroneal, tibialis anterior				
Below fibular	6	5.9	4.0	
Above fibular	9	11.5	4.0	16.1
Right peroneal, extensor digitorum brevis				
Ankle	9	NR	NR	
Right tibial, abductor hallucis				
Ankle	10	NR	NR	

From NeurologyContinuum
2022

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Hereditary Neuropathies

Genetically and phenotypically diverse

Most common: PMP22, GJB1, MPZ, GDAP1; though many genes

Core Features:

Chronic, very slowly progressive (often lifelong)

Distal symptoms with foot deformity

NCS- diffuse severe slow (no conduction block)

Often presents years after onset

Diagnosis: Genetic testing



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Case 3:

A 68-year-old man was referred to the neurology clinic for gait imbalance. He described an unsteady gait but no falls. Further questioning elicited reports of numbness and tightness in his feet, without neuropathic pain. The physical examination showed a mild length-dependent loss of vibration sense and light touch on the feet with preserved strength and reflexes. He was diagnosed with large fiber polyneuropathy, and workup revealed a serum IgM monoclonal gammopathy

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MGUS and neuropathy

MGUS is common, 3-4% of patients older than 50
Progression to MM is the main clinical consequence

Frequent association with neuropathy, 3-5% of patients with MGUS have neuropathy

10% of patients with otherwise idiopathic neuropathy will have MGUS
E.g. much often that would be expected for unrelated co-existing conditions

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Case 3:

A 68 yo M with gait imbalance. + Unsteady gait but no falls +numbness and tightness in his feet, w/o neuropathic pain. Exam=a mild length-dependent loss of vib and LT on the feet with preserved strength and reflexes. He was diagnosed with large fiber polyneuropathy, and WU revealed a serum IgM monoclonal gammopathy.

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Case 3 (cont.)

Returned 2 yrs later w/ recent dx of multiple myeloma and described severe worsening of his neuropathy. With detailed history taking, he recalled very slow mild progression of his neuropathy for 2 years but then a recent onset of excruciating burning pain and progressively worsening balance within 3 months of starting bortezomib. Exam revealed additional substantial loss of all sensory modalities and mild distal weakness. The initial differential diagnosis included worsening of his existing neuropathy related to monoclonal gammopathy or multiple myeloma versus bortezomib-related neuropathy. The neuropathy was suspected to be related to bortezomib use because of the temporal relationship between the onset of therapy and symptoms and the dramatic change in the neuropathy phenotype. After a conference call with the patient, oncologist, and neurologist, bortezomib was stopped for a month, and the neuropathy began to improve. Ultimately, the patient was switched to lenalidomide, and he recovered, albeit not entirely from his bortezomib-related neuropathy.

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Toxic Neuropathy

Medication-induced:

Chemotherapy (platinum, taxanes, vinca alkaloids, bortezomib), at times up to 30%

NB: immune checkpoint inhibitors may cause immune neuropathy, myasthenia, myositis;

Anti-retrovirals (older agents)

Alcoholic neuropathy

Occupational exposures:

Heavy metals (lead, thallium)

Organic solvents

Pesticides

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Toxic Neuropathy

Onset / Pace: Gradual / progressive course

Distribution: Distal length dependent

Modality: sensory > motor deficits, axonal

Often a cumulative effective. Diagnosis relies on careful history taking and a focus on timing of exposure vs symptoms



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Diabetic Neuropathy

Onset / Pace: Gradual / progressive course

Distribution: Distal length dependent

Modality: sensory > motor deficits, axonal

Often painful

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Diabetic Neuropathy

Electrodiagnostic testing is generally not necessary

Management

- 1) Control the diabetes
- 2) Healthy lifestyle – weight loss, diet, **exercise** e.g. treat **metabolic syndrome**

Glycemic control is required but not sufficient by itself to prevent neuropathy progression

- 3) Pain control

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Diabetic Neuropathy Pain- JAMA Jan 20, 2026

-Supplement: alpha lipoic acid 600-1200 mg a day

-Topicals: Lidocaine patch 1-3 patches per day, capsaicin, Tiger balm

- 1) Gabapentin 1200-3600 mg/d in 3 divided, Pregabalin 300-600 mg a day in 3 divided
- 2) SNRIs: Duloxetine 60-120 mg a day, venlafaxine 37.5-300 mg a day
- 3) TCAs: Amitriptyline 10 -75 mg a d, nortriptyline

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Autonomic Neuropathy

Presenting symptoms:

Orthostatic Hypotension

Constipation

Gastroparesis

Bladder dysfunction

Sexual dysfunction

Sweating changes



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Case 4:

A 30 year old man presented to the laboratory for diffuse, shock like pain. He had been diagnosed with type-1 diabetes as a teenager and historically had poor glycemic control. He recently decided to turn over a new leaf and had been seeking regular medical care over the past 3 months. Three weeks ago he developed burning and shock-like pain in his hands, feet and abdomen. On examination he has normal strength and vibration sensation, however severe pain to pin-prick in his hands and feet. On review of his lab testing his a1c was historically >15%, however most recently was 7%.

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Treatment-induced Neuropathy of Diabetes

Occurs in patients who are chronically hyperglycemic and then rapidly controlled

- impacts small fiber nerves with significant **pain**
- Nerve conductions are often normal (large fiber nerves not involved)

Tx=Stabilize glycemic control, aim for gradual a1c reduction and initiate neuropathic pain medications

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Diabetic Amyotrophy-

- Often occurs in patients with well controlled diabetes esp recent / rapid control
- Severe pain to hip or thigh with neuropathic features
- Weakness and atrophy
 - Involvement spreads beyond a single nerve or nerve root
- NCS shows axonal sensorimotor neuropathy; EMG shows denervation
- MRI plexus may be pursued to r/o malignancy or other compressive lesion

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Vasculitic Neuropathy

Onset / Pace: Subacute progressive;
Often stepwise

Distribution: Mononeuropathies Multiplex
Often asymmetric, with individual nerves being picked

Modality: Sensory and motor;

Often painful



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Vasculitic Neuropathy - evaluation

Nerve conduction and EMG

MRI Brain and Spinal Cord

CT chest and abdomen (if systemic vasculitis suspected)

Labwork

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Vasculitic Neuropathy - lab work

Extractable nuclear antigen antibodies (which includes the following: anti-Ro [also called CCP], anti-SBA, anti-La [also called anti-SB2], anti-Sm [anti-Smith antibody], anti-RNP, anti-RNP/anti-proteinase 3, anti-ly-1, anti-Scl70, anti-centromere)	C3
ANCA (proteinase 3, myeloperoxidase)	C4
Erythrocyte sedimentation rate	Hepatitis C virus
C-reactive protein	Hepatitis B virus
Cryoglobulin	Human immunodeficiency virus (HIV)
Complete blood cell count with differential, kidney function tests	Lyme disease
Liver function tests	Rheumatoid factor
Urinalysis	Antinuclear antibody
Urine protein	dsDNA
Serum protein electrophoresis/immunofixation electrophoresis	Nerve, muscle, kidney, pulmonary, skin, or salivary gland biopsy depending on organ involvement
Serum free light chain	
Hemoglobin A _{1c}	

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Vasculitic Neuropathy - Treatment

Refer to Rheumatology

- High dose steroids
- Rituximab (preferred) OR cyclophosphamide

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Vasculitic Neuropathy - Pain

Topicals: Lidocaine, capsaicin, tiger balm

Prescription Medications:

- 1) Gabapentinoids: Gabapentin, Pregabalin
- 2) SNRIs: Duloxetine, venlafaxine
- 3) TCAs: Amitriptyline, nortriptyline

Rarely: Oxcarbazepine, Lamotrigine (these usually do not work)

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Supplements

- Alpha lipoic acid 600 -1200 mg a day
- B12 2000 mcg/d
- Folate 1 mg a day
- B6 20 mg a day
- Coenzyme Q10 300 mg a day (less evidence)
- L carnitine 500 tid:



Supported for DPN in some reviews (500–1,000 mg three times daily), with benefit on neuropathic pain. However, in chemo-induced PN it was found likely ineffective or even harmful, so avoid in that setting.-

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Red Light Therapy



Red light therapy ("photobiomodulation") shows promising but low-to-moderate quality evidence for neuropathy

-may reduce pain/sensory symptoms in diabetic and chemo-induced neuropathy

-low-level laser therapy uses red ($\approx 630\text{--}670\text{ nm}$) and/or near-infrared ($\approx 780\text{--}904\text{ nm}$) light — this actually **does** reach deeper nerve targets

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Summary/Highlights

-Don't forget to order the SPEP as part of first line neuropathy labs.

-Red flags:

Subacute progression; greater than expected motor involvement; weakness in a mononeuropathies multiplex OR proximal + distal pattern; extensive pure sensory loss

Autonomic neuropathy could be the 1st sign of parkinsonism

-Alpha lipoic acid 600 -1200 mg a day

-B12 2000 mcg/d

-Folate 1 mg a day

-B6 20 mg a day

Coenzyme Q10 300 mg a day (less evidence)

-L carnitine 500 tid

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"To the world you may be one person, but to one person you may be the world."

-Dr. Seuss

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Nutritional Neuropathies

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