Evaluation of Peripheral Neuropathy

IN GENERAL symptoms of neuropathy in adults include paresthesias (sensory loss, tingling, burning) and/or clumsiness (weakness). These are due to lower motor neuron disease, therefore reflexes are usually absent.

In children, suspect neuropathy when gait is abnormal or motor milestones not reached. EMG is crucial to determine neuropathy vs myopathy in a child since myopathies are more common in childhood.
Evaluation of Peripheral Neuropathy

• THE EXAM
• HISTORY
• Be sure to understand what patient means by “unsteady”, “woozy”, “my legs don’t feel right”, “my legs don’t do what I want”
• Ask about positive sensory symptoms such as tingling, burning, electric shocks, shooting pain
Evaluation of Peripheral Neuropathy

- Other positive sensory symptoms: “sock feels bunched up”, “there is something in the shoe”
- Ask about negative sensory symptoms such as numbness
- Ask about clumsiness and tripping
- Ask about difficulty typing, knitting, loss of dexterity
- Ask about shortness of breath, weight loss, changes in hair or skin, thinning of muscles
Evaluation of Peripheral Neuropathy

Ask about medical conditions such as diabetes, thyroid disease, abdominal surgeries

• Ask about dietary habits, alcohol use
• Family history is extremely important: presentations and symptoms in family members with hereditary neuropathies can vary greatly
Evaluation of Peripheral Neuropathy

- Ask about present and past medications, exposure to heavy metals and chemicals

- PHYSICAL EXAM
  - Gait must be done with shoes and socks off
  - Look for deformities of the foot
  - Check muscles of the calves and thighs, sometimes the hands for atrophy and fasciculations
  - Look for weakness standing on toes and heels, lifting from the hip to walk
Evaluation of Peripheral Neuropathy

- Sensory exam: pin prick, vibration, position sense
- Romberg checks for dorsal column function
- Tandem walking is helpful if possible
- Reflexes are important and if present and especially abnormally brisk goes against a peripheral neuropathy (Hoffman and Babinski)
Evaluation of Peripheral Neuropathy

- HEREDITARY NEUROPATHY
- 2 groups: Hereditary Motor Sensory Neuropathy (HMSN I-III) and Hereditary Sensory Neuropathy (HSN I-IV)

- HMSN I (Charcot-Marie-Tooth Disease, Peroneal Muscular Atrophy, Roussy-Levy Syndrome)
- Autosomal dominant
- Variable penetrance
Evaluation of Peripheral Neuropathy

• Pes Cavus, club foot, wasting and weakness of peroneal muscles producing foot drop usually in the teens to 20’s
• Later, there is atrophy of the distal 1/3 of the thigh – stork leg or champagne bottle
• Vibration is impaired and later joint position sense, though motor impairment is more prominent
• In severe, long standing cases involvement of the hands is seen
Evaluation of Peripheral Neuropathy

- Roussy-Levy syndrome is similar, but has an essential tremor
- EMG shows profound slowing of motor conduction and even family members with no symptoms may have abnormal EMG conduction
- Survival is good and it is rare to progress to wheelchair
Evaluation of Peripheral Neuropathy

• HMSN II is identical to HMSN I but occurs later in life, usually in the 20’s to 30’s
• It is milder and affects only the legs and EMG conductions are minimally reduced
• HMSN III (Hypertrophic Peripheral, Dejerine-Sotas Disease)
• Autosomal recessive, begins in childhood
• Short stature, kyphosis and foot and hand deformities
Evaluation of Peripheral Neuropathy

- HSN I (Hereditary Sensory Neuropathy of Denny-Brown)
- Rare, autosomal dominant
- Begins in teens and 20’s
- Severe loss of temperature and pain sensation in legs
Evaluation of Peripheral Neuropathy

• HSN II (Morvan’s Syndrome, Infantile Syringomyelia, Congenital Sensory Neuropathy)
• Very rare, autosomal recessive, distal sensory deficits with deformities
• Same as HSN I, but onset in infancy

• HSN III (Riley-Day Syndrome, Familial Dysautonomia)
• Very rare, autosomal recessive seen in Jewish families
Evaluation of Peripheral Neuropathy

• Congenital absence of dorsal root neurons
• Severe autonomic neuropathy – fluctuating body temperatures, no tears, dry mouth, postural hypotension, impaired taste, SMOOTH tongue, absent reflexes
• Death is early by age 15

• HSN IV (Congenital Sensory Neuropathy with Loss of Sweating)
• Extremely rare, autosomal recessive
Evaluation of Peripheral Neuropathy

• Presents in infancy, high fevers, mental retardation and short stature, insensitivity to pain, poor prognosis

• METABOLIC NEUROPATHIES

• These are inherited, but biochemical defect has been identified, so they are classified separately
Evaluation of Peripheral Neuropathy

- **Amyloid Neuropathy**
- Direct deposition of amyloid around nerve fibers, covering the fibers and microvascular amyloid
- Damages small-diameter fibers – pain and temperature loss and autonomic neuropathy
- 4 varieties

- **Systemic Amyloidosis** can be complicated by a peripheral neuropathy

- **Primary Amyloidosis** (includes Multiple Myeloma) have generalized sensorimotor neuropathy
Evaluation of Peripheral Neuropathy

- Need to check biopsy of sural nerve, rectum or gum
- Death usually due to cardiac or renal amyloid

LIPOPROTEIN DISORDERS
- Very rare, cerebral degenerative disorders due to deposition of lipoproteins in brain
- **Metachromatic Leukodystrophy** – deficiency of arylsulfatase A.
- Sulfatides deposited in the brain causing demyelination
- Infantile, Juvenile and adult – all fatal in a few years
Evaluation of Peripheral Neuropathy

• **Krabbe’s Disease** – deficiency of galactosylceramide beta-galactosidase
  
  • Progressive cerebral degeneration, fatal within 1-2 years, onset in first year of life

• **Bassen-Kornzweig Syndrome** (A-betalipoproteinemia)
  
  • Autosomal dominant with triglycerides accumulating in intestinal mucosa impairing absorption of fat soluble vitamins
  
  • Malabsorption, developmental delay, ataxia, dysarthria
  
  • May be associated with Retinitis Pigmentosa
  
  • Extremely low cholesterol
  
  • Acanthocytes in blood
  
  • Live to middle age, treatment with fat restriction and vitamin supplementation delays symptoms
Evaluation of Peripheral Neuropathy

- **Tangier Disease** (High-Density Lipoprotein Deficiency)
- Autosomal recessive
- Deposition of cholesterol in tonsils (swollen, yellow tonsils interfere with breathing and swallowing)
- Extremely low cholesterol and high-density lipoproteins in serum
- Severe impairment of pain and temperature sensation mimicking syringomyelia
- Slowly progressive
Evaluation of Peripheral Neuropathy

- **Refsum’s Disease** (Hereditary Ataxic Neuropathy, Phytanic Acid Storage Disease)
  - Very rare, inability to break down phytanic acid in fish oils, dairy products and beef
  - Late teens, retinitis pigmentosa, deafness, ataxia
  - Fatal due to cardiac involvement

- **Fabry’s Disease** (Angiokeratoma Coporis Diffusum, Galactosidase A Deficiency)
  - X-linked recessive, abnormal lipids deposited in tissues
  - Telangiectatic rash lower trunk and upper legs
  - Severe, excruciating burning neuropathy
  - Death due to renal failure
Evaluation of Peripheral Neuropathy

• METABOLICALLY TRIGGERED NEUROPATHY

• Acute Intermittent Porphyria
  • Classic of six variants is due to abnormal porphyrin metabolism uroporphyrinogen-1 synthetase
  • Thought to be due to toxic metabolites
  • Attacks triggered by drugs, but also fever and fasting
Evaluation of Peripheral Neuropathy

- Many drugs no longer used, but can occur with the following:
  - Carbamazepine, Ergotamine derivatives, Imiprimine, Levodopa, Meprobamate, Estrogens, Phenytoin, Tolbutamide, Chlordiazepoxide
- Condition mimics others: UTI or abdominal pain
- Severe painful neuropathy without sensory loss, but if present it is in a swim trunk distribution
- If motor, can be ascending, areflexic paralysis with cranial nerve and autonomic involvement (mimics Guillain-Barre)
- Patients are frequently not believed, may have psychotic symptoms and emotional problems.
- Think of it in patients with surgical, neurological and psychiatric consultations.
Evaluation of Peripheral Neuropathy

- Diagnostic test is now direct erythrocyte urobinogen-1 synthetase
- Deep red urine only seen during an attack if urine is left out in the light and allowed to oxidize
- Secondary metabolic dysfunction with SIADH, salt losing nephropathy and liver damage
- High mortality 25-50% with paralysis and cerebral damage
- Slow recovery over 6-8 weeks and often incomplete
- Treat attacks with IV glucose and hematin
Evaluation of Peripheral Neuropathy

- INFECTIVE/AUTO-IMMUNE CAUSES OF NEUROPATHY
  - **Leprosy**
  - **Herpes Zoster**
  - **Diptheritic Neuropathy**
  - Rare due to vaccines, toxin impairs Schwann cells from making myelin
  - Occurs 4-6 weeks after infection
  - Rapidly ascending paralysis with respiratory involvement (mimics Guillain-Barre)
Evaluation of Peripheral Neuropathy

• Sarcoidosis
• Peripheral neuropathy in 5%
• Consider when there is bilateral Bell’s palsy or recurrent Bell’s
Evaluation of Peripheral Neuropathy

- **Acute Inflammatory Demyelinating Polyneuropathy (AIDP, Guillain-Barre Syndrome)**
- The classic syndrome described by Guillain and Barre is an ascending motor weakness which can affect all skeletal muscles including respiratory and bulbar.
- It can affect the autonomic nervous system with hypotension, hypertension or arrhythmias.
- However, there are many variants including Miller-Fisher which starts with the bulbar muscles. It may begin asymmetrically and have a more prominent sensory dysfunction with significant pain and paresthesias so AIDP is the better term.
Evaluation of Peripheral Neuropathy

• History of respiratory or GI viral illness 1-2 weeks before, may be seen with remote cancers
• Hallmark finding of absent reflexes out of proportion to the amount of weakness (ask if they have had reflexes in the past)
• CSF protein is high and EMG shows slowed conductions due to demyelination
• 10% mortality
• Treatment is IVIG for 5 days, must watch for HTN
• Plasmapheresis is beneficial similar to IVIG, but not always available
• Typically, patients get worse before getting better, may need intubation
• High proportion of patients not recovering completely
Evaluation of Peripheral Neuropathy

• Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
  • Slower progression than AIDP

• Chronic Relapsing Inflammatory Polyneuropathy (CRIP)
Evaluation of Peripheral Neuropathy

• TOXIC NEUROPATHIES
  
• Arsenic
• Lead
• Thallium – cockroach poison
• Tri-ortho-cresyl phosphate – flavoring agent in illicit alcohol during prohibition, more recently found in cooking oil from Morocco
• Organic solvents – glue sniffing
Evaluation of Peripheral Neuropathy

- **DRUG-INDUCED NEUROPATHY**
  - Thalidomide

- **Gold treatments**

- **Antibiotics**
  - Metronidazole long term use
  - Nitrofurantoin
  - Dapsone used to treat leprosy and pneumocystis carinii
  - Isoniazid and ethionamide for TB

- **Antineoplastic Agents**
  - Vinca alkaloids (lymphoma) cause painful neuropathy with wasting and weakness of hand muscles, rapid areflexia
  - Cisplatin (ovarian), but neuropathy can be a remote complication of ovarian cancer
Evaluation of Peripheral Neuropathy

- Phentoin
- Disulfuram
- Hydralazine
- Penicillin
- Perhexilitine
- Cliquinol
- Sodium Cyanate
- Pyridoxine (ironically used to prevent neuropathy in those taking Isoniazid)
Evaluation of Peripheral Neuropathy

- NEUROPATHIES DUE TO UNDERLYING MEDICAL CONDITIONS

- Alcoholic Peripheral Neuropathy
  - Not just due to a Vitamin B1 deficiency – replacement without stopping alcohol is not effective
  - Very painful neuropathy in the feet
  - Seen even in those who are not malnourished
  - Alcoholics are prone to pressure palsies
Evaluation of Peripheral Neuropathy

• DIABETIC PERIPHERAL NEUROPATHY
• Most common cause of peripheral neuropathy
• Neuropathy may present before diabetes is diagnosed in adult onset diabetes
• 50% of those with diabetes for 20 years or more will have some level of neuropathy, more common in men
• Affects all fibers: small, large and autonomic
• Severe pain, tingling, burning, electric shocks
• Loss of sensation leads to Charcot joints
• Tight glucose control is treatment, but not curative and symptoms continue
Evaluation of Peripheral Neuropathy

- **DIABETIC AMYOTROPHY**
- A presumed vascular lesion of the lumbar roots or proximal nerves (femoral)
- Usually in males, adult onset diabetes
- Excruciating pain in the anterior thigh
- May see dramatic weight loss
- Progressive weakness proximally with thigh muscle atrophy, loss of patella reflex
- Mimics femoral neuropathy or lumbar radiculitis
- Recovery in 6-18 months
Evaluation of Peripheral Neuropathy

- **ISCHEMIC PERIPHERAL NEUROPATHY**
- **Diabetes**
- **Collagen-vascular disorders** (polyarteritis nodosa)
  - Diffuse sensorimotor neuropathy or a mononeuritis multiplex
- **Lupus** — can mimic AIDP, diffuse sensorimotor neuropathy or mononeuritis multiplex
- Vascular and immune based
Evaluation of Peripheral Neuropathy

- MISCELLANEOUS

- Neuropathy of chronic renal failure

- Carcinoma-associated neuropathy – pure sensory due to damage of dorsal root ganglion

- Painful paresthesias and ataxia due to position sense loss

- Oat cell of the lung and ovarian

- Neuropathy may predate the tumor by years
Evaluation of Peripheral Neuropathy

- Lymphoma-associated neuropathy is sensorimotor, will improve with treatment of underlying lymphoma

- Myelomatosis

- Para-proteinemias

- Vitamin B12 deficiency
Evaluation of Peripheral Neuropathy

- Tests should include:
  - CBC, chemistries, SPEP, Vitamin B12, Phytanic level if suspected, TSH, ANA, ESR, RF, CH50, Lyme, 24 hour urine for heavy metals, CXR, breast and ovarian exams
  - EMG
Evaluation of Peripheral Neuropathy

- M.P. is a 58 y/o, L-H white woman
- Complex-partial seizures since age 22 (head injuries after falling off a horse at age 9 with LOC and age 16 without LOC)
- No warning, closes eyes and becomes limp, will fall if standing
- Occasional lip smacking
- Loses memory for the 15 minutes before the seizure and never regains it
- Associated with menstrual cycle
- Last 30 seconds to 1.5 minutes
- Lethargic afterward
Evaluation of Peripheral Neuropathy

- Treated with Dilantin since onset
- Came to me May 2008 because of seizures
- PMH: HTN, embolic strokes 3/08, hyperlipidemia
- MEDS: Dilantin 200/260, HCTZ, Atenolol, Aspirin 325mg, Simvastatin, Ferrous Sulfate
- SOCIAL HX: married, no children, not working, never smoked, no alcohol
- FAMILY HX: Aunt with DVT, Mother 3 miscarriages
- LABS: Previous antiphospholipid antibodies reportedly negative, B12 303, Dilantin 12.9, normal CBC, Chems.
- Increased Dilantin to 490mg per day
Evaluation of Peripheral Neuropathy

• 2009 added Lamictal due to continued seizures
• Hysterectomy 4/09
• August 2009 presented with complaints of feet feeling cold, bottoms hurting when not wearing shoes, numbness feet to knees, feels she will lose balance; numbness in fingers and increased sensitivity in fingers
• Had these for about 2 years since starting Atenolol and HCTZ and read that these could cause paresthesias, but they were now worse
Evaluation of Peripheral Neuropathy

- **EXAM:** normal pin prick; vibration decreased in great toes and finger tips; position sense decreased in left great toe

- **LABS:** fasting glucose 105; HgbA1c 5.3; Vitamin B12 204; TSH 0.58; ESR 13, Mg, Lyme, ANA, RF were normal

- Dilantin can cause neuropathy – taper to off and add Keppra

- Developed headache, diarrhea and hair loss with Keppra – changed to Gabapentin
Evaluation of Peripheral Neuropathy

- October 2009: numb left foot and fingers
- EXAM: positive Romberg, could not tandem walk well

- January 2010: dropping things, numbness in toes and fingers, left hand tingling with use and stiff in the morning
- EXAM: positive left wrist Tinel’s; slow gait with positive Romberg, could not tandem walk well
- Planned wrist splint and give more time off Dilantin
Evaluation of Peripheral Neuropathy

- May 2010: numbness in feet to knees; tingling left hand; numbness in fingers
- CK, cholesterol, TSH, chemistries, CBC all normal
- No weakness; absent vibration in legs; minimally present in fingers; pin prick intact; position sense decreased in toes; positive Romberg, wide based gait
Evaluation of Peripheral Neuropathy

• June 2010: EMG shows sensorimotor demyelinating polyneuropathy in hands and feet (slowed conductions, decreased amplitudes and prolonged latencies)

• October 2010: Referred to neuromuscular specialists – findings more consistent with familial CMT-1 vs an inflammatory neuropathy

• Checked CMT DNA which was negative, now considering CIDP
Evaluation of Peripheral Neuropathy

- May 2011 EMG: Similar findings
- IVIG started in May – once a month for 3 months
- Checked SPEP – negative
- July 2011 repeat EMG: no change
- Started Azathioprine and Prednisone
- 8/14/14: continued improvement in strength, numbness, gait
- Continuing Azathioprine and Prednisone
Evaluation of Peripheral Neuropathy

• 55 y/o, R-H white man seen in November 2012
• 2 month history of pain in left leg, radiating from lower back into hip region; intense tingling and pain that he could not sleep at night
• He is a very active runner and cyclist and noted weakness in left leg running and walking. He could not lift the thigh to climb stairs or put on his pants; sometimes dragging the left leg when running; rare knee buckling
• Patch of numbness above the left knee and in left thigh, tingling in medial left thigh
• Seeing a chiropractor and pain is better
• MRI unremarkable; CT pelvis possible hemangioma
Evaluation of Peripheral Neuropathy

- No symptoms in right leg or arms; no bladder or bowel changes; no injuries
- Still walked 9 miles per day without pain
- PMH: Diabetes type I; HTN, hyperlipidemia
- MEDS: Vytorin, Lisinopril, Lantus and Humalog Insulins
- Social HX: never smoked, no alcohol, married, works for IBM
- Family Hx: no diabetes
Evaluation of Peripheral Neuropathy

• EXAM: moderate left hip flexion and knee extension weakness; mild left hip adduction weakness
• Reflexes difficult to obtain throughout
• Pin prick decreased in left lateral femoral cutaneous distribution, intact in feet; light touch, proprioception and vibration were intact
• Romberg was negative and gait intact
Evaluation of Peripheral Neuropathy

- December 2012: EMG shows prolonged distal latencies in left arm and leg with decreased amplitudes and conduction velocities
- Needle exam shows decreased recruitment in left lateral and medial quad
- He is noticing fasciculations when exercising
- January 2013 referred to neuromuscular specialists (I wanted to rule out ALS)
- Had lost 16 pounds, wasting noticed in quads
- Weakness in quads and hip flexion; reflexes decreased; pin prick decreased in feet to the ankle; fasciculations
• EMG together with MRI and presentation consistent with diabetic amyotrophy

• We had been using Lyrica, then Gabapentin for pain (he could not tolerate Cymbalta)

• Last visit January 2014 – off medication, strength almost totally back to normal with mild numbness left lower thigh

• New symptom of numbness in left hand, positive Tinel’s – possible Carpal Tunnel Syndrome (diabetics are more prone to the pressure palsies)