“Doc, DO I Have Neuropathy?”

Stanley Jones P. Iyadurai, MSc, PhD, MD
Assistant Professor of Neurology
Neuromuscular Division, Department of Neurology
The Ohio State University Wexner Medical Center

Case Vignettes

Susan, 50	Gwenn, 32	John, 52	Sally, 42
DM – 12 yrs	Hypothyroidism	No PMH	No PMH
B/N/T – 2 yrs	N/T at night 3 months	B/N/T – 6 days	B/N/T – few months
Hands, Feet	Right hand	Hands, Arms Feet, Legs	Hands, Feet Burning Pain
Arms, Legs	Difficulty Opening jars	Pain Breathing	Pain Redness
Imbalance	Normal gait	Imbalance	Normal Strength

“Neuropathy” - Definition

- ***“Neuron” and “Pathos”*** **(Greek)**
- **Disease of the Peripheral Nerve**
- **Dysfunction of the nerves outside of the central nervous system**

Neuropathy - General Theme

- **Symmetric**
- **Insidious**
- **More prominent distally and starts in legs**
- **Involves both motor and sensory components**
- **May cause pain**
- **May cause loss of balance**
- **Progressive, but not debilitating**

Not all that tingles is neuropathy

‘numbness and tingling’

- **not all numbness and tingling is peripheral nerve**
  - **RLS**
  - **edema**
  - **deconditioning**
  - **central nervous system**
  - **nerve root [‘sciatica’]**

Classification - Functional

- **Motor – affects the motor nerves ➔ Weakness**
- **Sensory**
  - **Pain**
  - **Small Fiber**
  - **Large Fiber**
  - **Large and Small Fiber**
  - **Neuronopathy (ganglionopathy)**
- **Autonomic**
  - **Sweating Changes, Blood Pressure Changes**

Classification – Time-course

- Acute
  - Immune-mediated
- Infantile Weakness
- Childhood-onset
- Relapsing
- Hereditary
  - Motor-Sensory
  - Motor Syndromes
  - Sensory Syndromes

Classification – Time-course

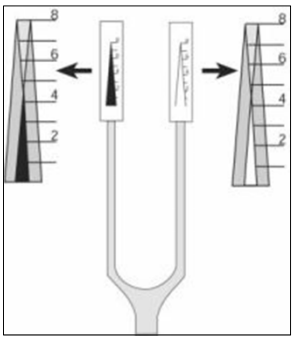
- Congenital/Hereditary
- Acquired
  - Reversible?
  - Demyelinating?
  - Immune-mediated?
  - Systemic diseases?

Neuropathy - Evaluation

- Detailed History
- Family History
- Clinical Examination
- Blood Work
- Special Tests – EMG/NCS
- Special Tests – Imaging
- Special Tests – Nerve/Muscle/Skin Biopsy

Examination

- Vibration sense – the most sensitive test
- Quantitative Tuning Fork (Rydel-Seiffer)
- Pin scratch test (gradient)
- Proprioception
- Temperature sense – comparisons
- Reflexes
- Distal strength testing
  - "Bring your toes up"
  - "Curl your toes down"
  - "Spread your toes"



“Doc, DO I Have Neuropathy?”

Amro Stino, MD
Assistant Professor-Clinical
Division of Neurology
The Ohio State University Wexner Medical Center

Work-up

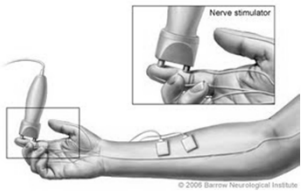
- **CBC, CMP, LFTs**
- **ESR, CRP, RF, ANA, ENA, ANCAs, ACE**
- **Hgb A1c, fasting glucose, 2h glucose tolerance, TSH, T3, T4, B12, MMA, B6, B1, D**
- **Lyme titer, RPR, HIV, Hepatitis panel,**
- **Quantitative immunoglobulins, Special antibodies**
- **immunofixation electrophoresis**
- **CSF**
- **EMG/NCS, consider MRI Brain/Spine, CT-C,A,P**
- **Nerve/muscle biopsy, Skin biopsy*, Autonomic testing***

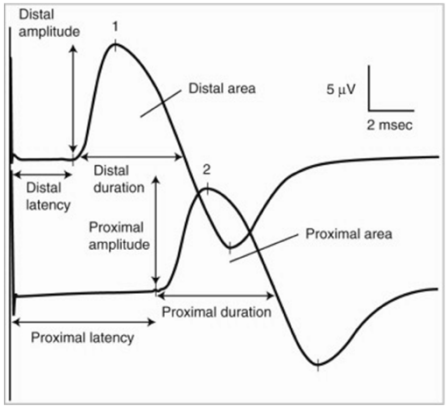
***consider if EMG/NCS normal**

‘The Big 4’ – The Most Common

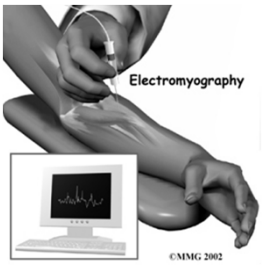
- **Diabetes AND impaired glucose tolerance**
  - **A1c, 2h glucose tolerance test, fasting glucose**
- **B12 deficiency**
  - **B12 + MMA**
- **Alcohol**
  - **CAGE questionnaire**
- **Plasma cell dyscrasias (paraproteinemias) –**
  - **immunofixation electrophoresis**

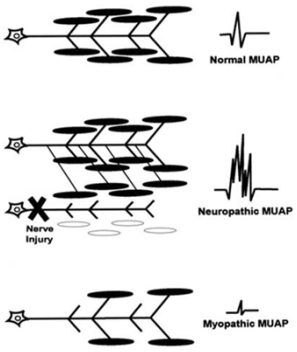
Nerve Conduction Studies (NCS)

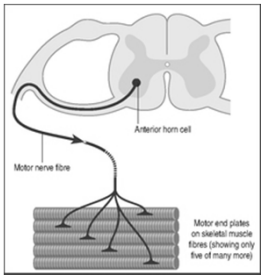




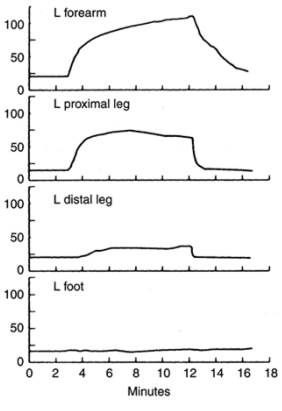
Electromyography (EMG)

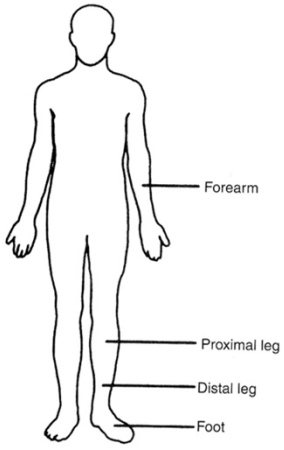






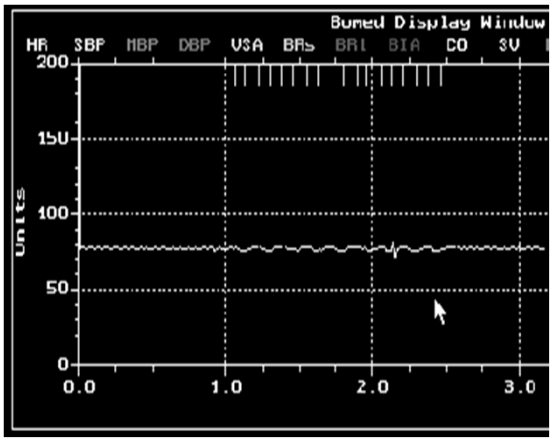
Autonomic testing – sweat output as measure of small fiber neuropathy = QSART





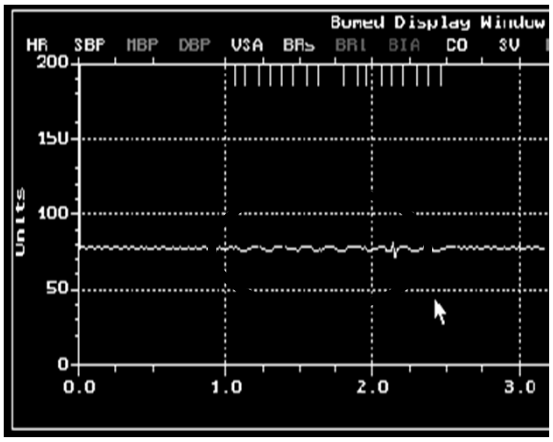
LENGTH DEPENDENT SWEAT LOSS – DISTAL IS < 1/3 PROXIMAL SWEAT VOLUME

Autonomic Testing - Loss of Heart Rate Variation to Deep Breathing = Cardiac wall remodeling in diabetics = Poor Prognosis



Courtesy of Brent Goodman, MD

Autonomic Testing - Loss of Heart Rate Variation to Deep Breathing = Cardiac wall remodeling in diabetics = Poor Prognosis



Virtually no heart rate variation

Courtesy of Brent Goodman, MD

“Doc, DO I Have Neuropathy?”

Stanley Jones P. Iyadurai, MSc, PhD, MD
Assistant Professor of Neurology
Neuromuscular Division, Department of Neurology
The Ohio State University Wexner Medical Center

Why Do We Care About Details?

- **Not to Miss a Treatable Cause**
- **Not to Miss an Immune-mediated Neuropathy – since it is often treatable**
- **Prevent Further Worsening of Neuropathy**

Causes

- Metabolic
- Vitamin deficiencies
- Inflammatory conditions
- Infections
- Cancer
- Drugs, Toxins
- Nerve injury at specific locations
- Immune Mediated Neuropathies
- Genetic

Metabolic

- Diabetes
- Thyroid
- Uremic (usually on hemodialysis)

Vitamin Deficiencies

- **Vitamin B12**
- **Vitamin B6**
- **Vitamin B1**
- **Vitamin E**

Inflammatory conditions

- **Vasculitides – often are very painful, multifocal, and require nerve and muscle biopsy. Treated with steroids and immunosuppressants**

EVALUATE FOR SECONDARY CAUSES

- **Systemic Lupus Erythematosus**
- **Celiac Sprue-related Neuropathy**
- **Connective Tissue Disorders**
- **Sarcoidosis**

Infections

- **HIV**
- **Hepatitis**
- **Lyme disease**
- **Leprosy**

Cancer

- **Due to any cancer in general**
- **Lymphoma**
- **Multiple Myeloma**
- **Result of Cancer Treatments**
- **Paraneoplastic – Specifically anti-Hu**

Paraproteinemias

- **MGUS – often mimics CIDP (demyelinating)**
- **Waldenstrom – more axonal**
- **Amyloidosis – get significant autonomic disturbance**
- **Multiple Myeloma – neuropathy usually results more from chemotherapy (bortezomib)**
- **POEMS – Polyneuropathy, Organomegaly, Endocrinopathy, M-protein Spike, Skin Changes.**

Drugs, Toxins

- **Chemotherapy drugs**
- **Amiodarone**
- **Dilantin**
- **Disulfiram**
- **Dapsone, Ethambutol**
- **Leflunomide**
- **Alcohol**
- **“Huffing”**
- **Agent Orange**

Nerve Injuries

- Carpal Tunnel
- Ulnar Neuropathy
- Common Peroneal Neuropathy

Immune-Mediated Neuropathies

- Evaluation based on specific antibodies in the serum
- Common ones: anti-GM-1, anti-GQ1b, anti-tubulin and anti-Hu, anti-TS-HDS
- Treatment is related to immune therapies and immunomodulation
- IVIG, Plasmapheresis, Steroids, Rituximab

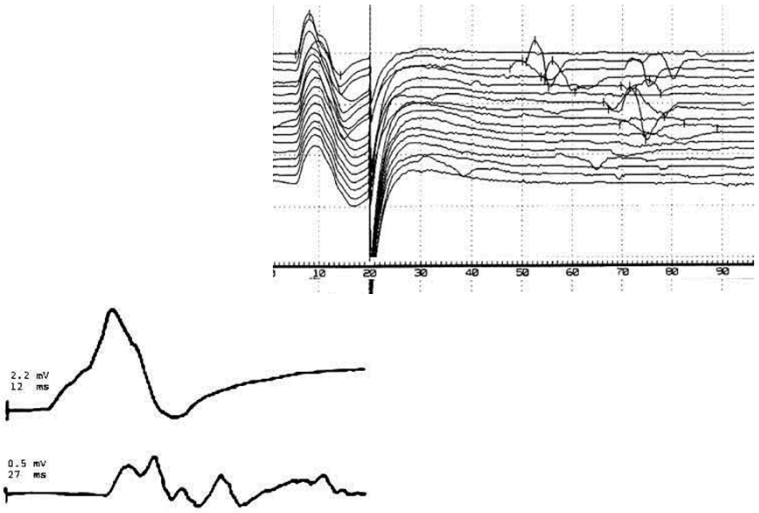
“Doc, DO I Have Neuropathy?”

Amro Stino, MD
Assistant Professor-Clinical
Division of Neurology
The Ohio State University Wexner Medical Center

Autoimmune Neuropathy Spectrum

- **Acquired, Immune Mediated Neuropathies**
  - **GBS – reaches nadir in < 4 weeks**
  - **CIDP – reaches nadir in > 8 weeks**

Acquired Demyelinating Features



Pictures from neuromuscular.wustl.edu, courtesy of Dr. Alan Pestronk

Typical GBS (AIDP)

- 90% + of GBS have AIDP presentation
- Sensory phase of 3 - 10 days
  - Numbness, tingling, tightness
  - Pain in 75-90%: often in the lower back or proximal legs
- Weakness spreads from legs to arms
  - Facial involvement in about 50% of otherwise typical cases
  - DTRs decreased to absent –
    - not always global
- Autonomic involvement in ~ 70% (may be severe)
  - Requires ICU stay
- 25-40% require ventilator assistance (may be very rapid)
  - 1/3 require intubation
  - Predictors of impending respiratory failure may prompt PLEX instead of IVIG to allow for faster treatment response

GBS Diagnostic Criteria

Necessary Criteria	Supportive Criteria
Symmetric weakness	Sensory sx./signs
Areflexia	CN weakness (VII)
Progression < 4 weeks	ANS dysfunction
	High CSF protein
	Demyelinating EPS

GBS Overview

Typical

- **Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP)**

Atypical

- **Acute Motor Axonal Neuropathy (AMAN)**
- **Acute Motor Sensory Axonal Neuropathy (AMSAN)**

Both AMAN and AMSAN have association with GD1a and GM1

- **Miller Fisher Variant (MFS) – GQ1b**
- **Pharyngeal Cervical Variant – GT1a**

GBS Treatment

- **Responds to IVIG or Plasmapheresis**

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

- **Chronic progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months and**
  - **Absent or reduced reflexes in all extremities**

CIDP Supportive Findings

1. **Elevated CSF protein with leukocyte count < 10/mm (level A)**
2. **MRI showing GAD enhancement and/or hypertrophy of cauda, lumbosacral, or cervical nerve roots, or brachial or lumbosacral plexus (level C)**
3. **Abnormal sensory electrophysiology in at least one nerve (good practice point)**
    1. **Normal sural with abnormal median (excluding CTS) or radial SNAP**
    2. **CV < 80% of LLN (<70% if SNAP amplitude <80% of LLN)**
    3. **Delayed SSEPs without CNS disease**

CIDP Treatment

- **Responds to IVIG, Steroids, or Plasmapheresis**

Multifocal Motor Neuropathy

- Associated with anti-GM1 IgM antibodies
- Antibodies bind to node of Ranvier structures of motor axons (GM1 enriched) and fix complement.
- Incidence: 0.6/100K
- Clinically:
  - non-contiguous motor nerves affected
  - weakness far in excess of atrophy noted (in distinction to MND)
  - asymmetric upper limb onset without sensory complaints
  - 20-30% can have brisk tendon reflexes
  - Combining galatocerbroside with GM1 increases sensitivity to 75%

Neuropathy – Treatment Principles

- Address Reversible Causes of Neuropathy
  - B12 deficiency - 2000mcg daily by mouth or IM
  - B6 toxicity – reduce amount
  - Alcohol abuse – abstinence, vitamin replenishment
- Pain Management – Try different classes +/- Tramadol before going to Opiates
  - Tricyclics
  - SNRIs
  - Sodium Channel Blockers
  - Calcium Channel Blockers
  - Tramadol
  - Opiates (long-acting)

Treatment

- **Anticonvulsants**
  - **Gabapentin**
  - **Pregabalin**
  - **Topiramate**
  - **Lamotrigine**
  - **Carbamazepine**
  - **Oxcarbazepine**

Treatment

- **Antidepressants**
  - **Amitriptyline (TCA)**
  - **Nortriptyline (TCA)**
  - **Desipramine (TCA)**
  - **Duloxetine (SNRI)**
  - **SSRIs**

Treatment

- Topical Anesthetics
  - 5% Lidocaine patch
  - 0.075% Capsaicin patch
- Opioids
  - Tramadol
  - Oxycodone

Common Mimics

- RLS
  - Requip
  - Check Ferritin
- PLMS
  - Sleep study

“Doc, DO I Have Neuropathy?”

Stanley Jones P. Iyadurai, MSc, PhD, MD
Assistant Professor of Neurology
Neuromuscular Division, Department of Neurology
The Ohio State University Wexner Medical Center

Case Presentation

- **54-year old man presents to the ER with recent onset of numbness and tingling in bilateral hands and feet (“stocking-glove distribution”)**

- **Examination – Reportedly Normal**
- **Blood sugar – 127 (Elevated)**
- **Diagnosis?**

Case presentation (Cont'd)

- **Diagnosis: "Diabetic neuropathy"**
  - **Start metformin**
- **2 days later, "increased numbness, worse tingling, and with pain"**
- **Examination with diminished reflexes**
  - **Diagnosis: ?**

Case Follow-up

- **CSF: Protein elevated at 124**
- **Diagnosis: Guillain-Barre Syndrome**
  - **IVIg treatment with full remission**

Genetic causes

- Suggested by a very long course
- No treatable reason found despite repetitive evaluation
- Loss of strength (motor nerves damaged) without much reported sensory loss (usually)
- Pain < dysfunction
- Family history

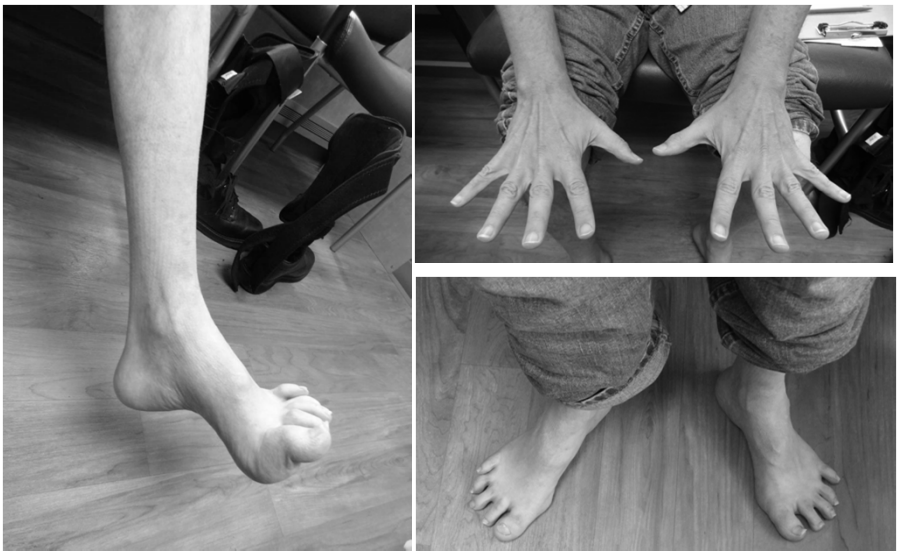
Genetic causes

- Charcot-Marie-Tooth disease
  - Many forms, many genes
- HNPP (PMP-22)
  - “Tool-belt” pressure causing pain and weakness
  - “Foot drop”
- Porphyria
- Amyloidosis

Rare genetic causes

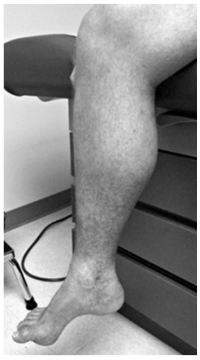
- **Fabry's disease (alpha-galactosidase)**
- **Metachromatic leukodystrophy (aryl sulfatase)**
- **Adrenoleukodystrophy**
- **Refsum's disease (phytanic acid)**

Hereditary Neuropathies

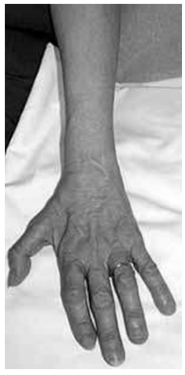


Neuropathic Gait

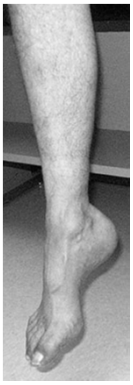
Hereditary Neuropathies



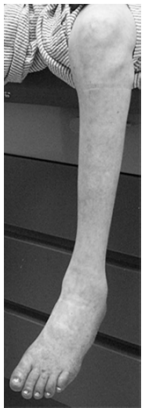
Chronic sensory neuropathy
High arches & Hammer toes
Preserved gastrocnemius size



CMT 1A
PMP-22
duplication



CMT 1X



CMT 2A2

Pictures from neuromuscular.wustl.edu, courtesy of Dr. Alan Pestronk

Case Vignettes

Susan, 50	Gwenn, 32	John, 52	Sally, 42
DM – 12 yrs	Hypothyroidism	No PMH	No PMH
B/N/T – 2 yrs	N/T at night 3 months	B/N/T – 6 days	B/N/T – few months
Hands, Feet	Right hand	Hands, Arms Feet, Legs	Hands, Feet Burning Pain
Arms, Legs	Difficulty Opening jars	Pain Breathing	Pain Redness
Imbalance	Normal gait	Imbalance	Normal Strength

Case Vignettes

Susan, 50	Gwenn, 32	John, 52	Sally, 42
DM – 12 yrs	Hypothyroidism	No PMH	No PMH
B/N/T – 2 yrs	N/T at night 3 months	B/N/T – 6 days	B/N/T – few months
Hands, Feet	Right hand	Hands, Arms Feet, Legs	Hands, Feet Burning Pain
Arms, Legs	Difficulty Opening jars	Pain Breathing	Pain Redness
Imbalance	Normal gait	Imbalance	Normal Strength
Diabetic Neuropathy			

Case Vignettes

Susan, 50	Gwenn, 32	John, 52	Sally, 42
DM – 12 yrs	Hypothyroidism	No PMH	No PMH
B/N/T – 2 yrs	N/T at night 3 months	B/N/T – 6 days	B/N/T – few months
Hands, Feet	Right hand	Hands, Arms Feet, Legs	Hands, Feet Burning Pain
Arms, Legs	Difficulty Opening jars	Pain Breathing	Pain Redness
Imbalance	Normal gait	Imbalance	Normal Strength
Diabetic Neuropathy	Carpal Tunnel Syndrome		

Case Vignettes

Susan, 50	Gwenn, 32	John, 52	Sally, 42
DM – 12 yrs	Hypothyroidism	No PMH	No PMH
B/N/T – 2 yrs	N/T at night 3 months	B/N/T – 6 days	B/N/T – few months
Hands, Feet	Right hand	Hands, Arms Feet, Legs	Hands, Feet Burning Pain
Arms, Legs	Difficulty Opening jars	Pain Breathing	Pain Redness
Imbalance	Normal gait	Imbalance	Normal Strength
Diabetic Neuropathy	Carpal Tunnel Syndrome	Guillain-Barre Syndrome	

Case Vignettes

Susan, 50	Gwenn, 32	John, 52	Sally, 42
DM – 12 yrs	Hypothyroidism	No PMH	No PMH
B/N/T – 2 yrs	N/T at night 3 months	B/N/T – 6 days	B/N/T – few months
Hands, Feet	Right hand	Hands, Arms Feet, Legs	Hands, Feet Burning Pain
Arms, Legs	Difficulty Opening jars	Pain Breathing	Pain Redness
Imbalance	Normal gait	Imbalance	Normal Strength
Diabetic Neuropathy	Carpal Tunnel Syndrome	Guillain-Barre Syndrome	Small Fiber Neuropathy