# A Working Neurologist's Thoughts on Peripheral Neuropathy 2019

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There are no relevant financial relationships with commercial interests to disclose

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# Swedish-Kadlec ALS Clinic

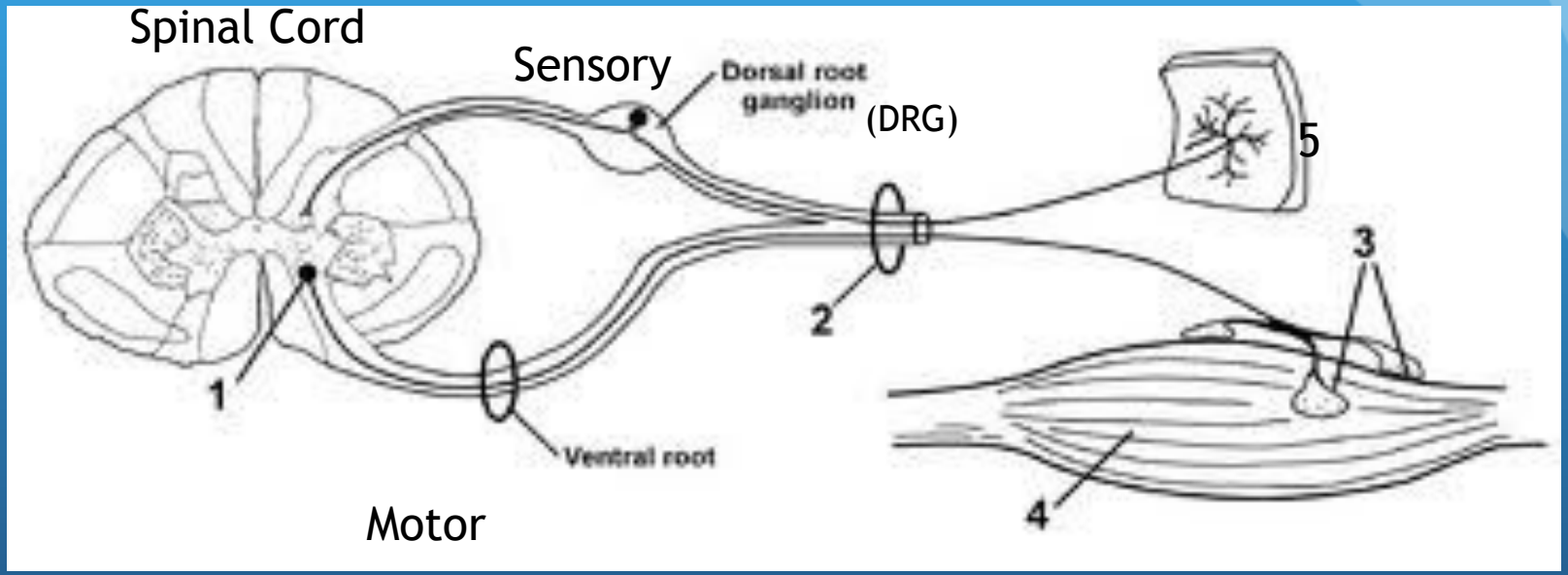
- I would like to point out we have a joint project with our Swedish ALS Clinic and with Kadlec Hospital.

# Peripheral Neuropathy

Disease or Dysfunction of Peripheral Nerves

1. Most common is distal symmetric sensory in feet, numb and-or pain.
2. Mono-neuropathies (carpal tunnel, ulnar neuropathy)
3. Plexopathies
4. Radiculopathies
5. Autonomic Neuropathies (often a component of other neuropathies)

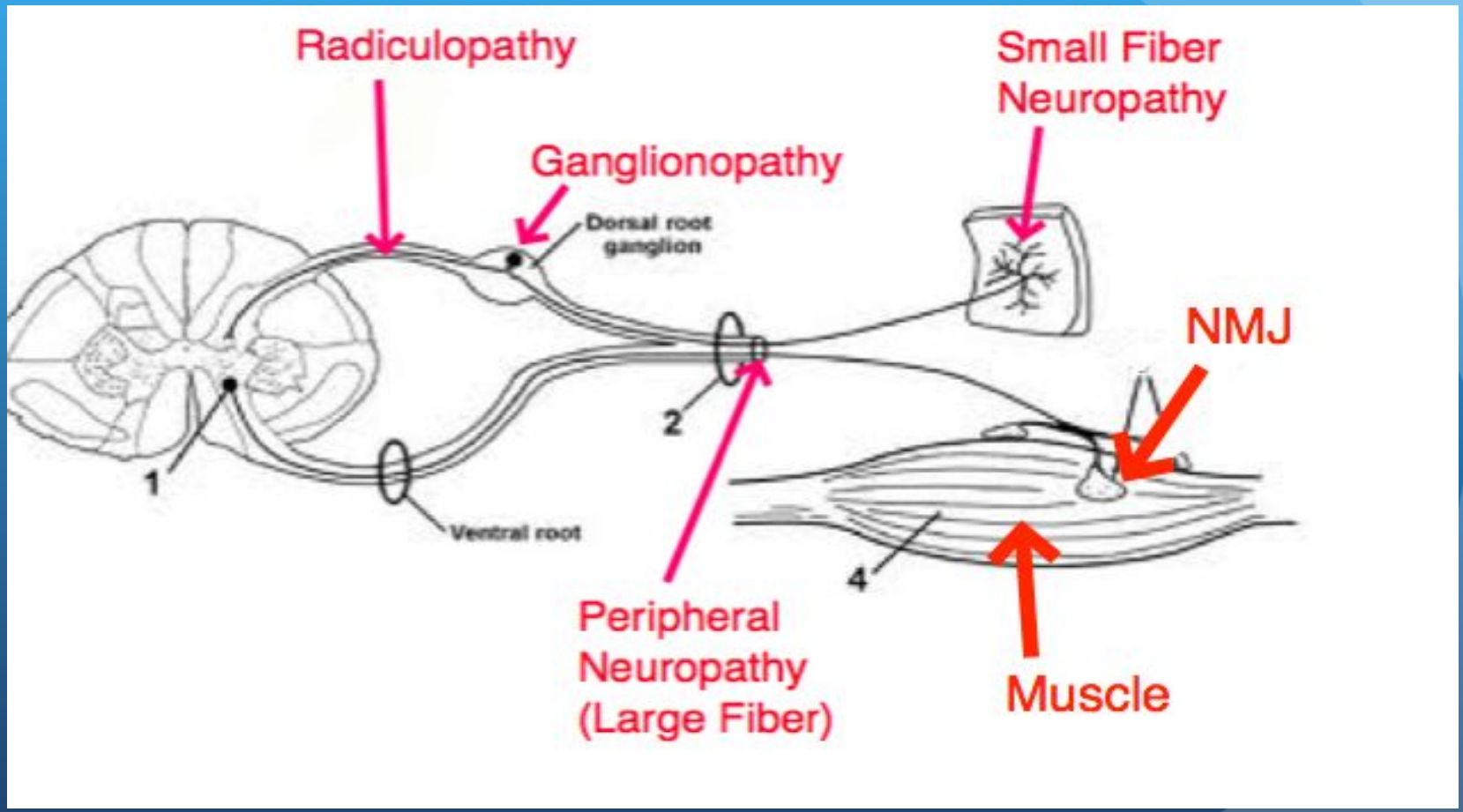
# Structure of a nerve root:
# Motor & Sensory Components




1. Anterior Horn Cell (Motor)
2. Nerve (motor and sensory axons
3. Neuromuscular junction
4. Muscle

Neuroanatomy.wisc.edu

# Location of Diseases



# Incidence and Prevalence

- Incidence of 77 per 100,000 per year
- Prevalence
  - 5.5% definite
  - 13.1% possible-probable-definite (mainly older than age 50)
  - 30% over age 80.


- Viss NA Neurology 2015 84(3) 259-65
- Hanewinckel R Neurology 2016 87:1892-98.

# There are a number of ways to think about neuropathy

- Patterns (sensory, sensorimotor, motor, autonomic, distal, symmetric-asymmetric).
- Biology (axonal, demyelinating, small fiber, nodal)
- Causes (diabetes, toxins-alcohol, hereditary, autoimmune, infiltrative-amyloidosis, infection-leprosy)

# So the rest of the talk:

- We should start with a frequent patient, and an exam and lab work-up.
- Then discuss nerve anatomy and types of neuropathies
- Then a brief review of EMN-NCS and what it is good for.
- Then talk about various specific neuropathies:
  - Diabetic variants
  - Toxins (alcohol, chemotherapies)
  - Mono-neuropathies
  - B12
  - Demyelinating neuropathies (Guillain Barre and a host of variants)
  - Para-proteinemias
  - Multi-focal mononeuropathies (vasculitis, MMN)
  - Inherited Neuropathies

# In practice, this is the majority of what you will see:

A distal symmetric neuropathy – often in toes and feet, numbness or a degree of pins and needles or burning pain. A mild sense of weakness, a mild sense of dysautonomia (resting tachycardia, light-headedness).

One third will relate to diabetes (or diabetes with metabolic syndrome).

One third will be unexplained.

One third is due to everything else.

# Diabetes and Metabolic Syndrome

- About 50% of type-2 diabetics will have some neuropathy symptoms after 10 years. [Ang L, Curr Diab Rep 2014: 528; Pop-Busui R, Diabetes Care 2013: 36:3208-15]
- Metabolic Syndrome worsens neuropathy independent of glycemic control. [Callaghan BC Diabetes 2016 39(5): 801-7; Costa LA Diabet Med 2004 21(3): 252-5, and several other studies]
- Enhanced glycemic control does not improve neuropathy (but you should do it anyway) [Callaghan BC, Cochrane Database, 2012:6]
- The American Diabetes Association has a position paper recommending treating the whole Metabolic Syndrome, not just sugar. Pop-Rusui R, Diabetes Care 2017; 40(1):136-54

# A 67 year old female walks in discussing numbness in toes and wobbliness.

- History.  Is it gradual or rapid, symmetric-asymmetric, at the end of the legs-feet or elsewhere.  Ask of course for diabetes, kidney disease, alcoholism, chemotherapy, family history.
- Exam steps
  - Gait – hold a tandem gait, Romberg (eyes closed, hands around body)
  - Strength testing (especially distal limbs), look for asymmetry
  - Vibration (128 Hz tuning fork, on the bone)
  - Monofilaments – or a q-tip
  - Pinprick (I use a small safety pin and throw it away)
  - Reflexes – especially ankles

# You need to add up a number of pieces.

- History about 7%
- Tuning fork 128 Hz on toes (on bone) about 33%
- Microfilaments or q-tip about 33%
- Loss of ankle reflex about 25%
- If you add these together for a sensory neuropathy (often diabetic) the accuracy is about 90%
- However: if there are major motor findings it is easier to explain, but the workup should be more aggressive.

--Michelle Mauermann, MD at Mayo Clinic

# Ways to evaluate this

- History
- Exam
  - Gait
  - Strength testing
  - Vibration (128 Hz tuning fork, on the bone – can be reduced in the elderly)
  - Monofilaments (or a q-tip)
  - Pinprick (I use a small safety pin and throw it away)
  - Reflexes – if ankle reflexes are present it is encouraging
- EMG-NCS (electromyography and nerve conduction studies)

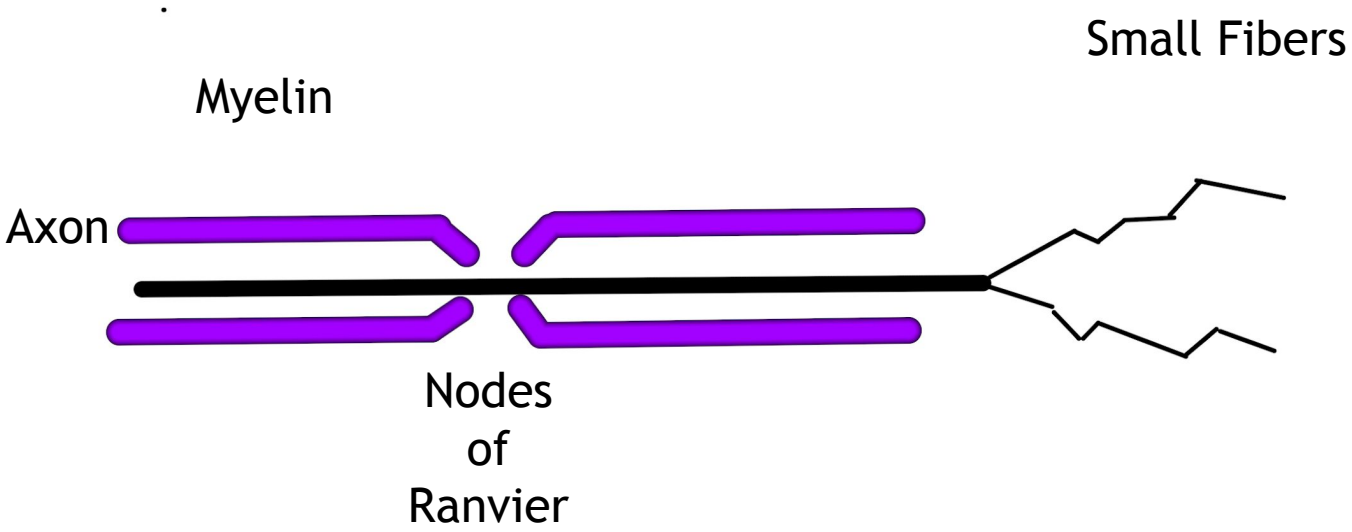
# A good lab workup

- Glucose
  - If glucose normal, add a glucose challenge test (2 hour) and-or A1c
- Renal Panel
- CBC
- ESR
- B12 and also Methylmalonic Acid (increases sensitivity)
- B6 (excess B6 can cause a neuropathy) and occasionally B1
- TSH
- Para-proteinemias:
  - Serum Protein Electrophoresis (SPEP)
  - AND ALSO: Serum Immunofixation (SPEP alone may miss 30% of IgM Monoclonal Ab, which are more prevalent in neuropathy.
- If there is a Risk: HIV, Lyme (prefer Western Blot)
- If a strong family history: the genetic panels have become less expensive (usually private labs)

# Even if a person has diabetes:

If the neuropathy symptoms or findings are significant, I often do this panel anyway in case there is a separate cause.

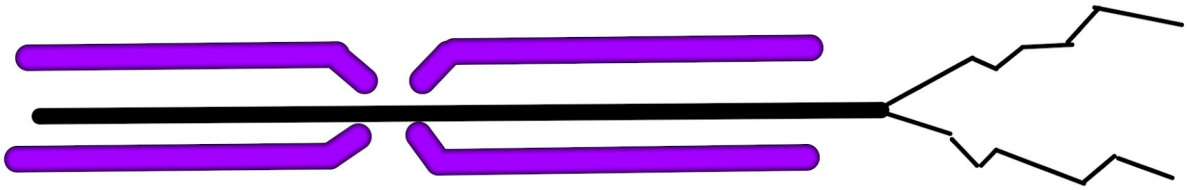
# Basic Nerve Anatomy



# Basic Nerve Anatomy

Demyelinating:
Guillain-Barre
CIDP, MADSAM, DADS
POEMS
Charcot Marie Tooth 1,3,4

Small Fiber[A-delta or C-fibers]:
Diabetes, Idiopathic, Leprosy
Sjogren's, HIV, Celiac,
Amyloidosis, Sarcoid,
Paraneoplastic-Anti-Hu



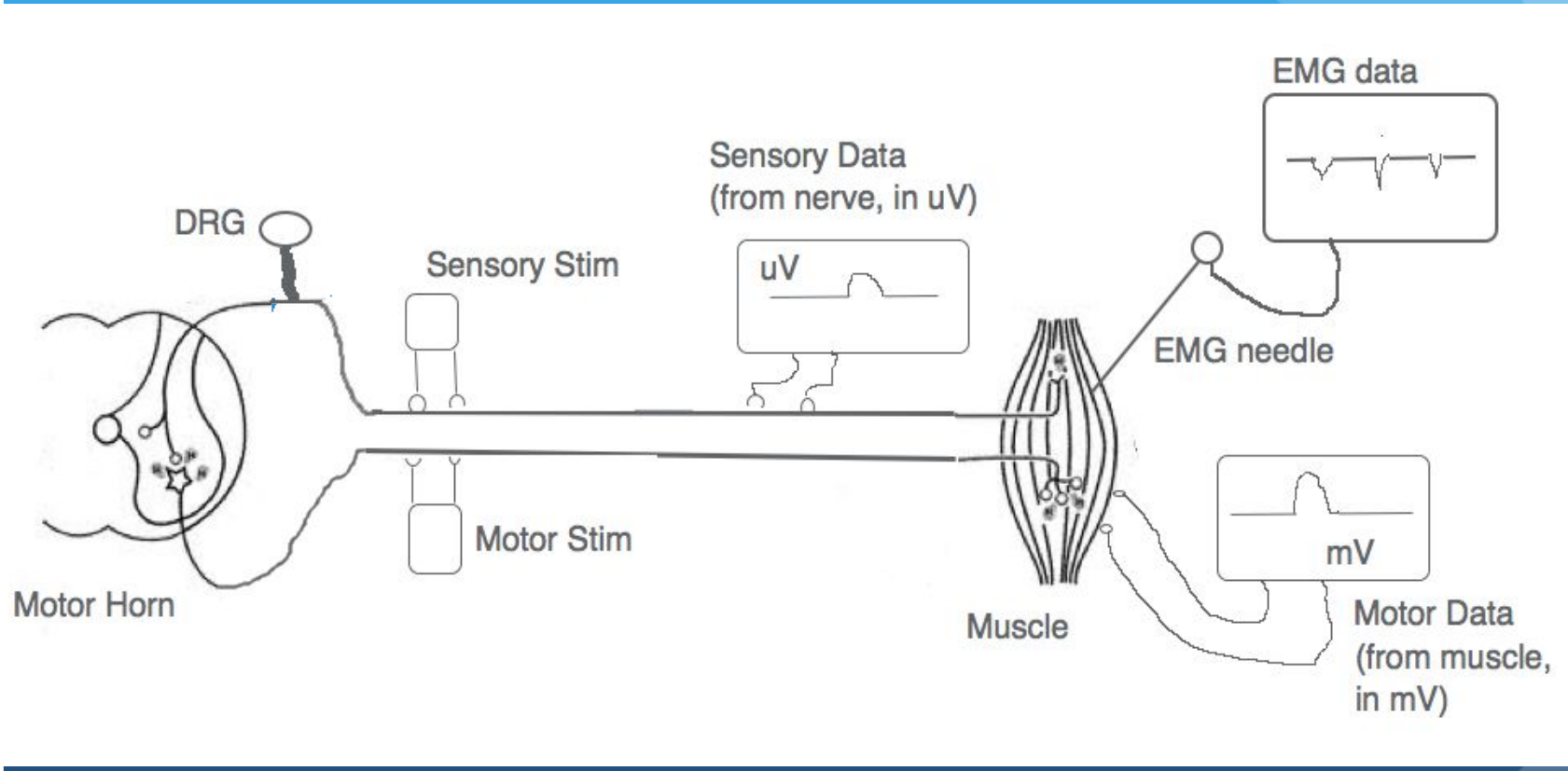
Axonal:
Diabetes
Idiopathic
Toxin-alcohol
B12, HIV,
Shingles
Sjogren's
Sarcoid
Kidney Failure
etc

Nodal:
AMAN (acute motor axonal variant of GBS)
Miller Fisher
MMN (multifocal motor neuropathy)

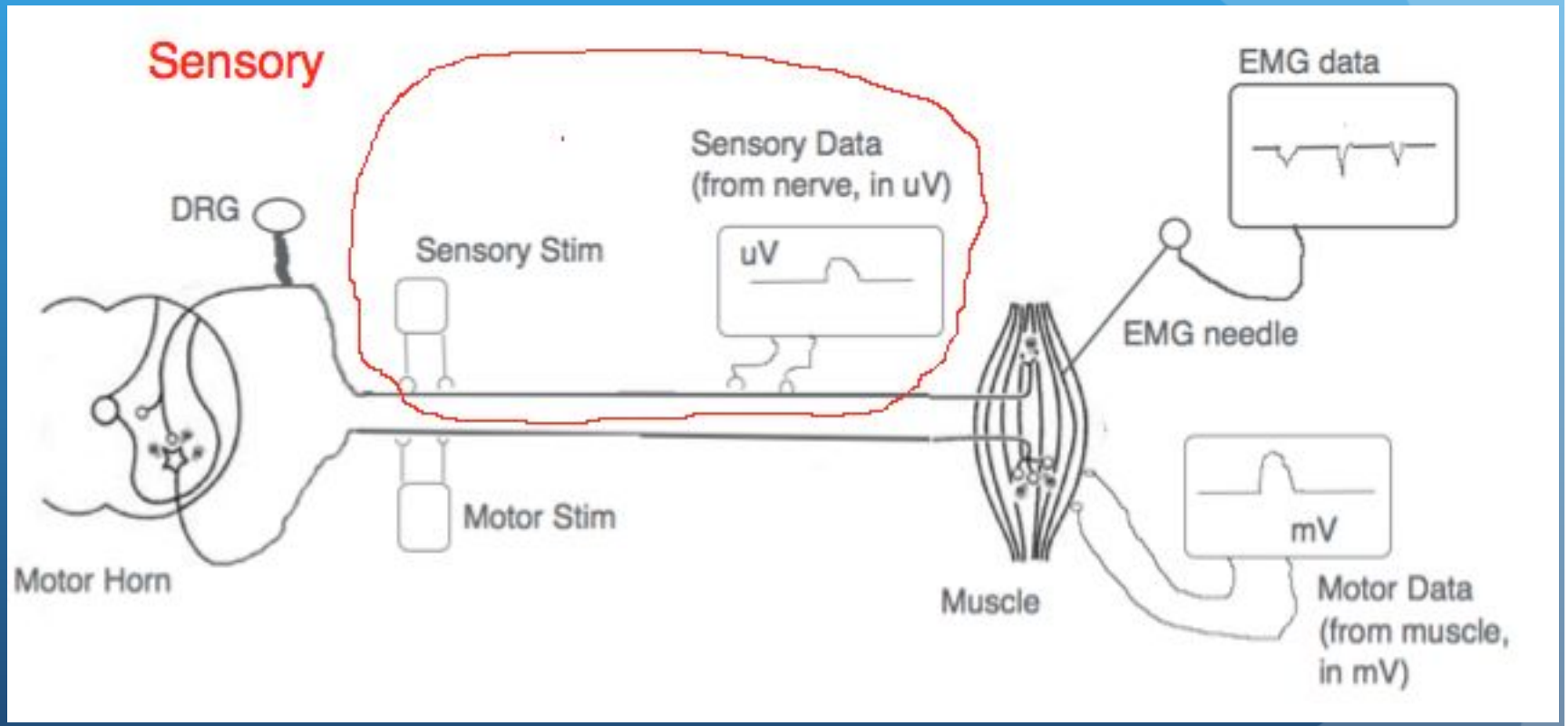
# Differences between Large Fiber and Small Fiber Neuropathies

| | Large Fiber (alpha motor, a-alpha/beta sensory -vibration and touch | Small Fiber (a-delta or c-fibers, pain and temperature) |
|---|---|---|
| Painful | sometimes | Common (allodynia) |
| Numbness | light touch, vibration | pinprick, temperature |
| Proprioception-Ataxia | late in course | No |
| Weakness | possible, mild to severe | No |
| Reflexes | reduced, often distal | Normal |
| EMG-NCS | Abnormal | Normal |

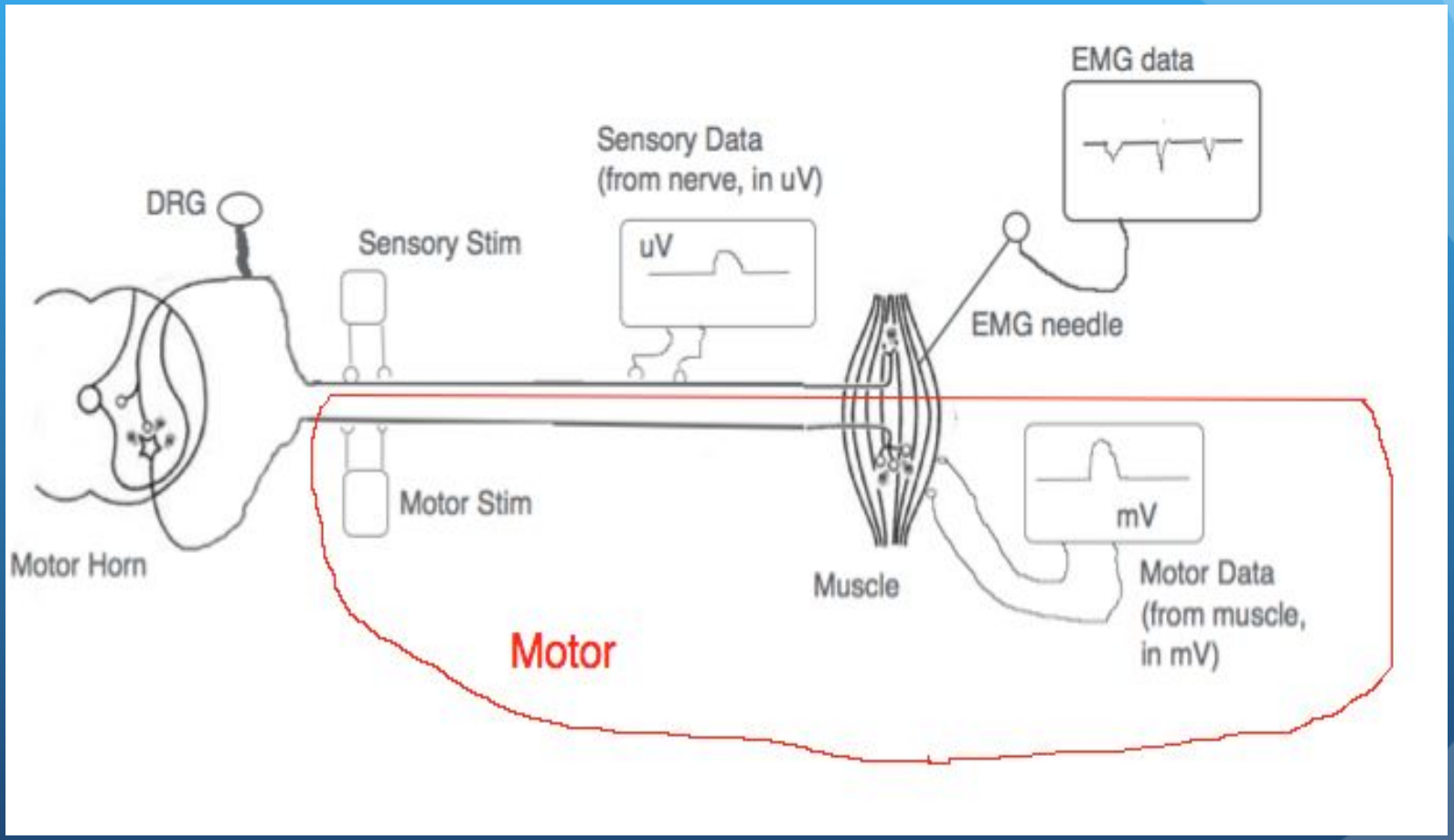
# Brief review of EMG-NCS Testing



# Sensory nerve conduction studies

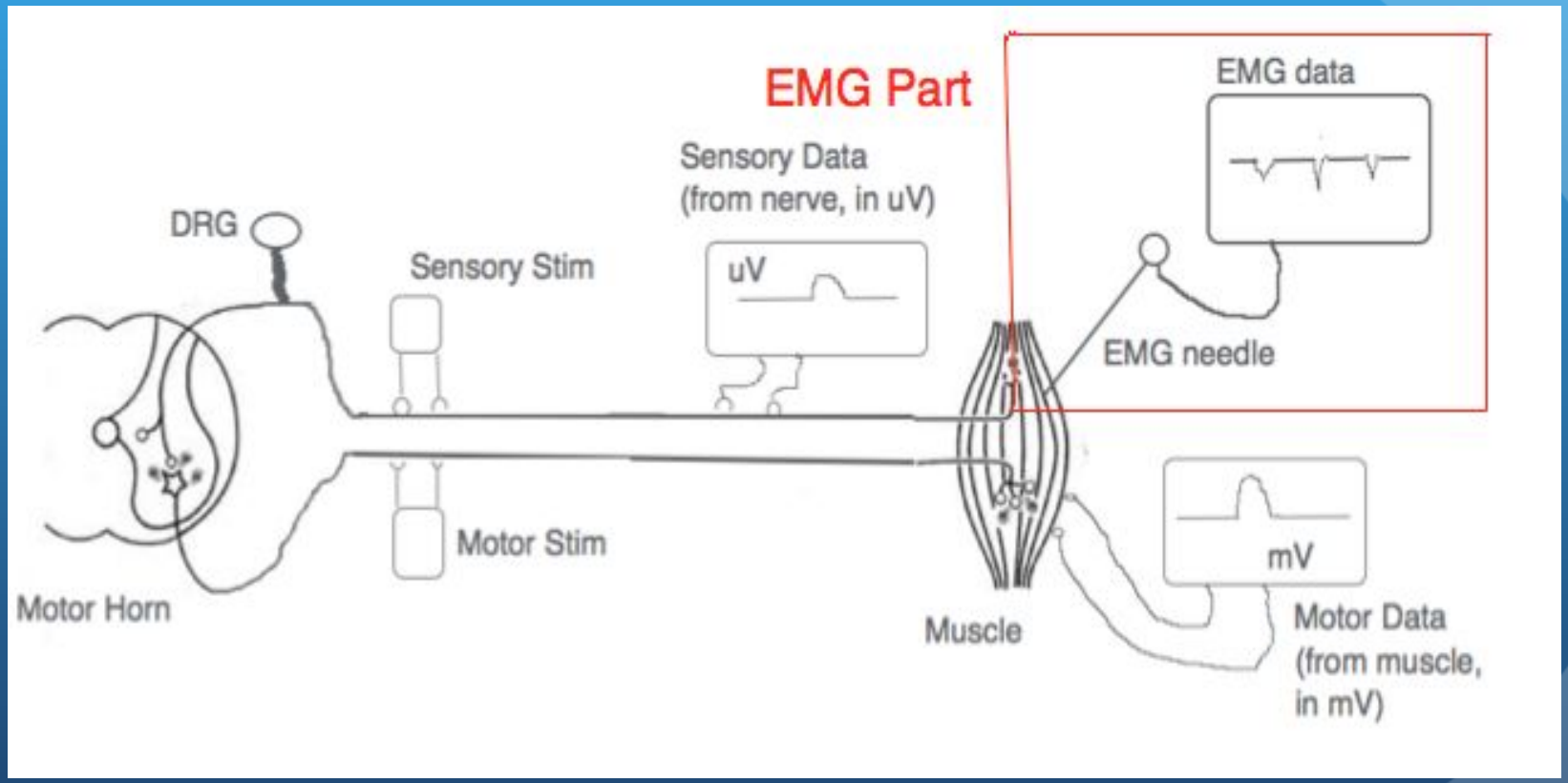


# Motor nerve conductions

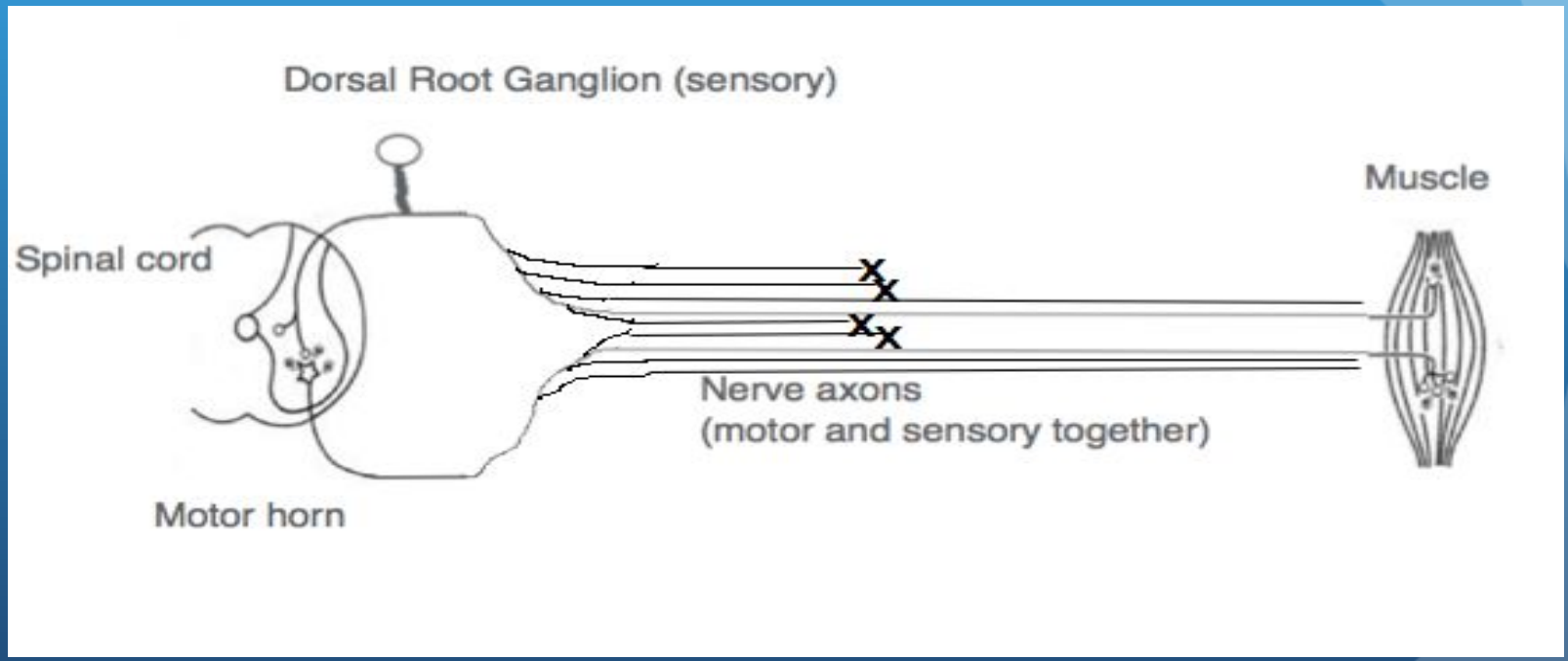


# EMG needle exam tests

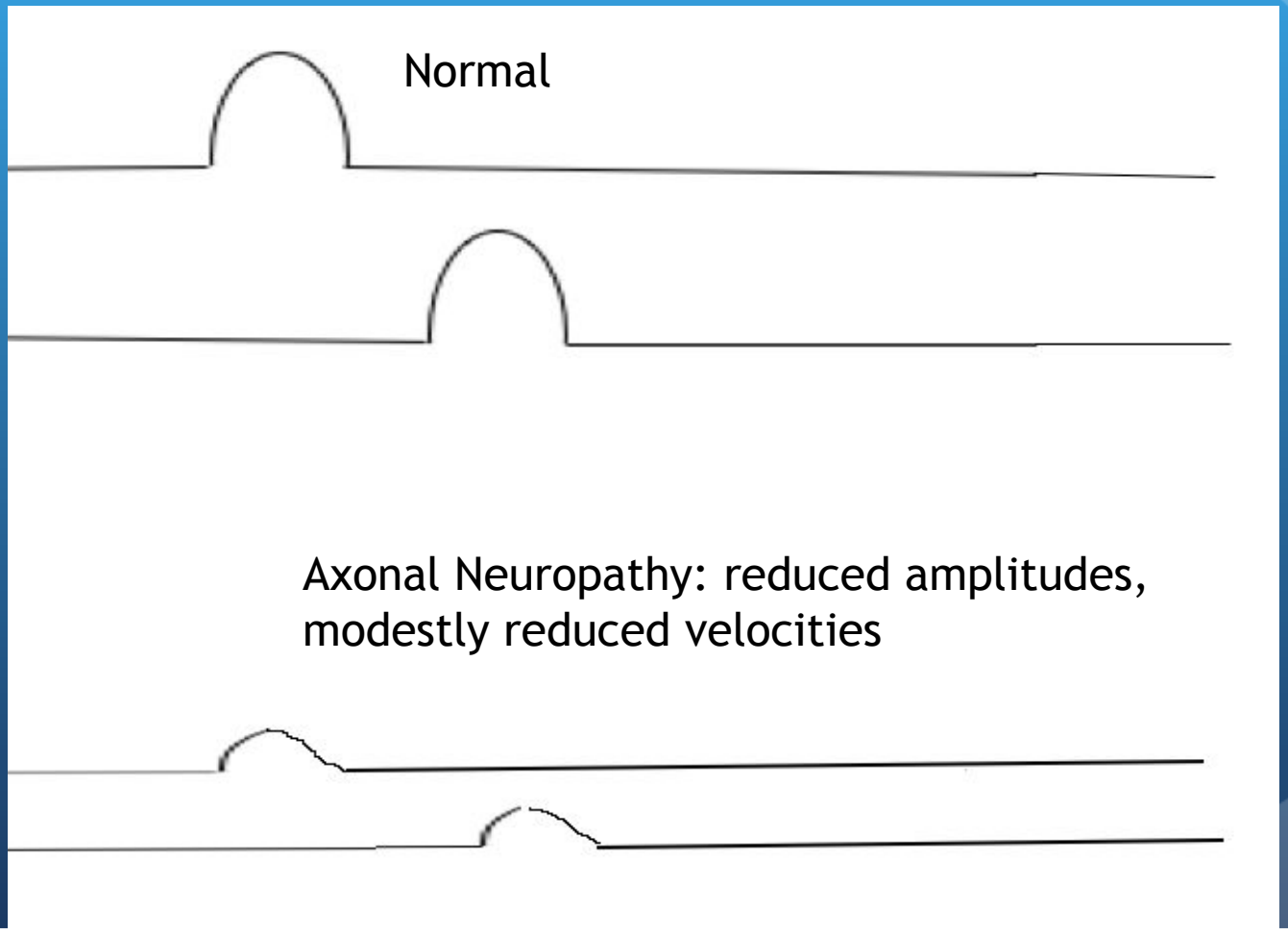
– mainly shows evidence of motor axonal loss



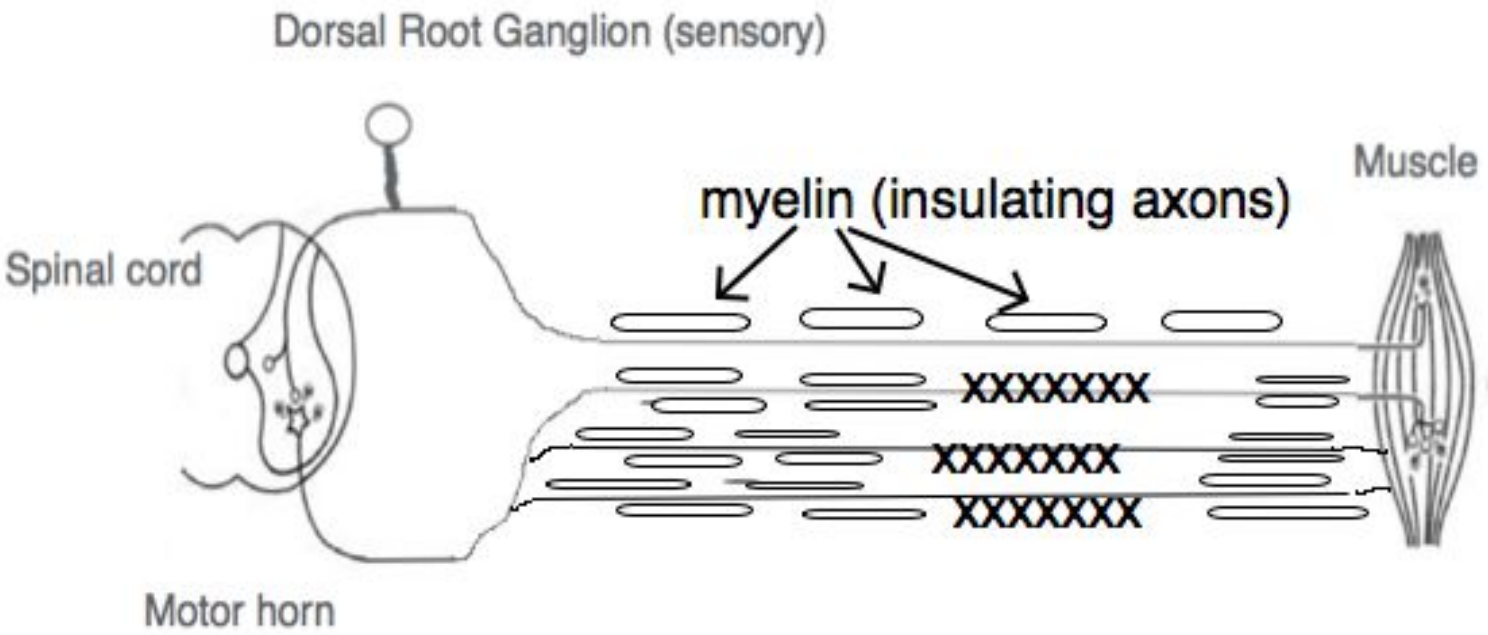
# Axonal Neuropathy (the most common neuropathy – alcohol, diabetes, toxins, etc)



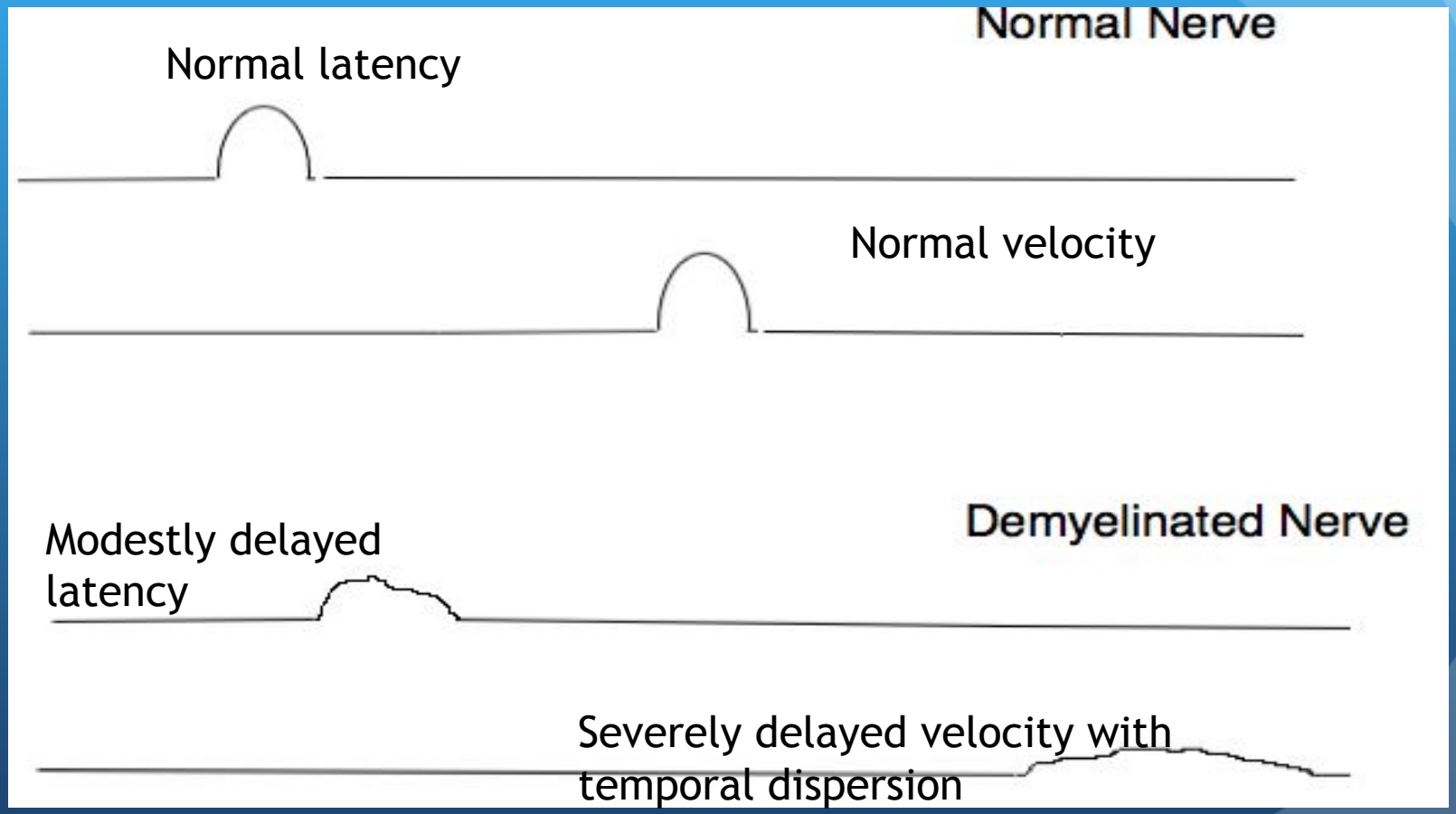
# Motor NCS: Normal versus Axonal Neuropathy



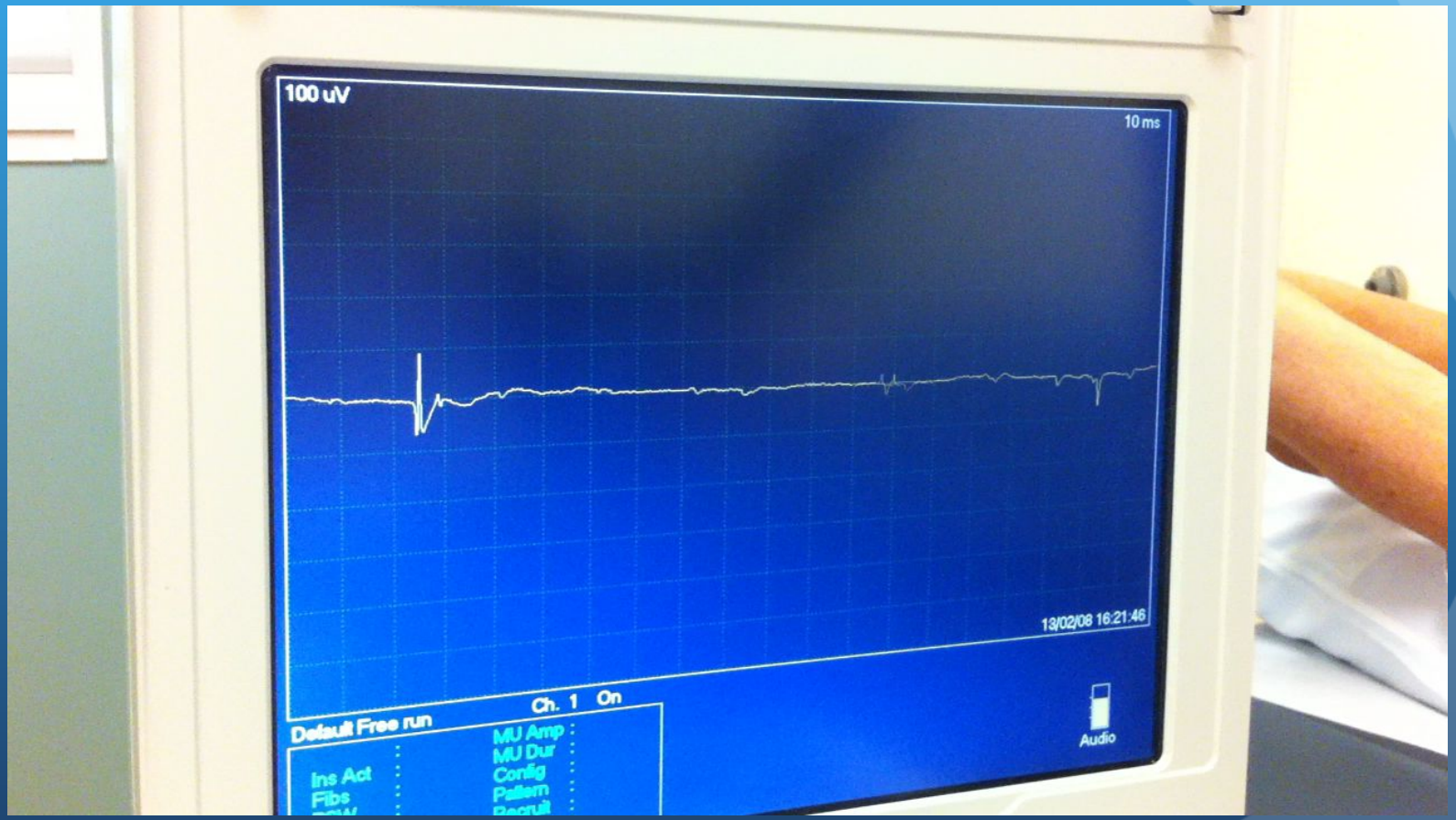
# Example 2: Demyelinating Neuropathy (less common)



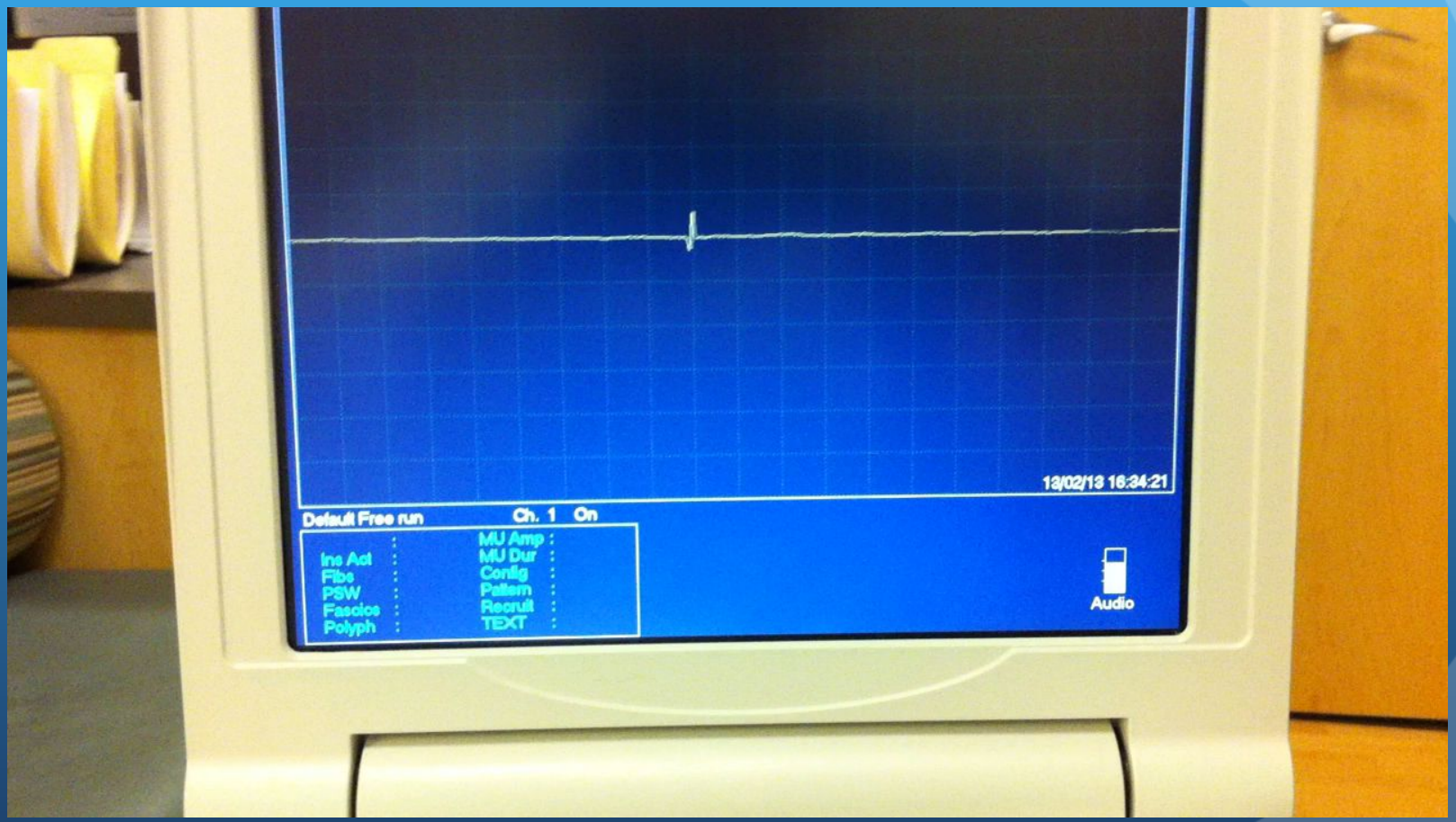
# Example: Demyelinating Neuropathy



# Sharp waves and fibrillations

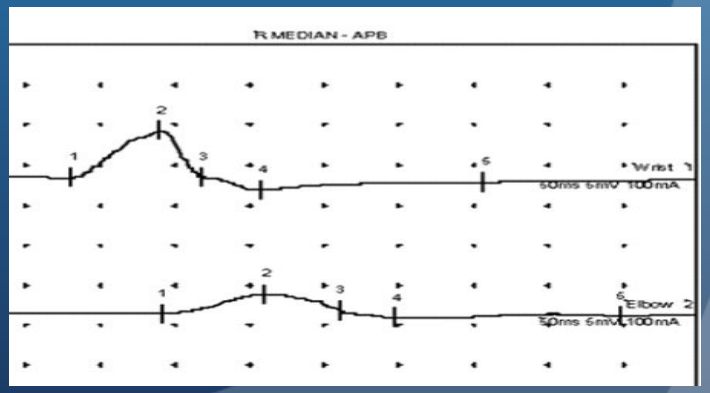


# Abnormal EMG: spikes, waves and reduced recruitment



# A couple of cautions about EMG

- EMG changes may not be present until 6 weeks after insult
- Cold Limbs slow velocities and can give a false positive
- Motor NCS are read from muscles. Elderly people may have limited foot muscles, which may be a false positive for amplitude.
- Elderly may lack distal lower sural (ankle) responses, even if normal.
- Demyelination: Several formulas
  - Best if motor velocity < 80% LLN, or if low amplitude < 70% LLN.
  - Temporal dispersion reinforces this
  - [Mallik A, J NN&P 2005, 76:ii23-1131]



# Standard Diabetic Neuropathy

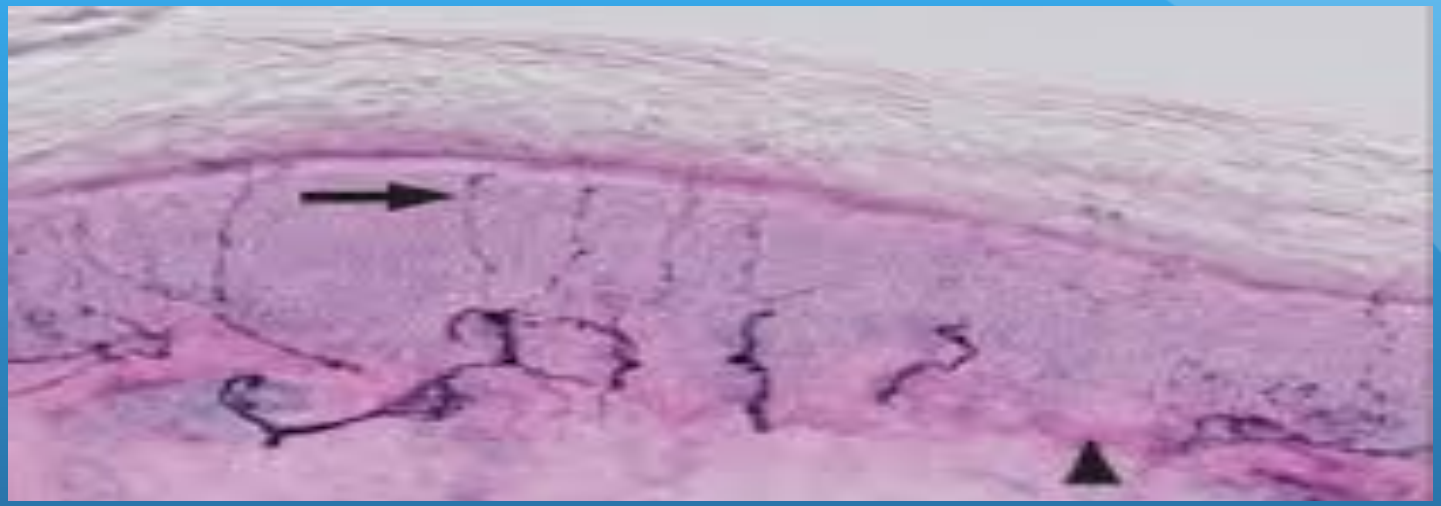
- Diabetes
  - Large fiber sensory neuropathy, 33% of all neuropathies
  - About 10-25% of diabetic neuropathies are small fiber, but may advance to large fiber
- Metabolic Syndrome with or without Diabetes
  - Impaired glucose tolerance (meaning a glucose challenge test) likely increases risk of painful neuropathy
  - So a concern is to treat the Metabolic Syndrome and Diabetes

# Comment on small fiber neuropathies

- Clinically length dependent with distal burning pain, numbness, paresthesias. May later advance to large fiber.
- Etiology similar to large fiber: diabetes,idiopathic, then several others (Sarcoid, Amyloid, Sjogren's, toxins, etc)
- The EMG-NCS, by definition, is normal in small fiber neuropathies
  - Skin Fiber Biopsies
  - QSART (a part of autonomic testing)
- But there is some evidence that there may be pathology at at the dorsal root ganglion, which is an ongoing area of research.

- [Chan AC, Muscle & Nerve 2016; 53(5):671-82; Khoshnoodi MA JAMA 2016; 73(6):684-90; Rolyan H Mol Pain 2016; 7:12.]

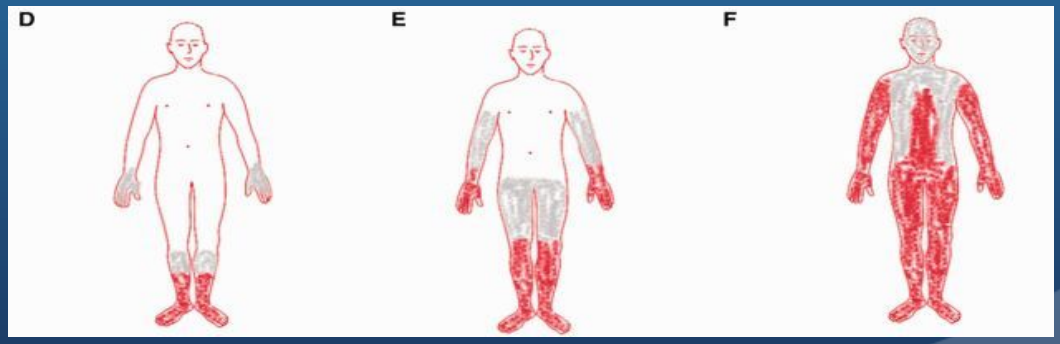
# A small fiber neuropathy biopsy



- Bunch biopsies: upper thigh, low ankle, done in office
- Done by private companies (several companies, often Fed-Ex to lab)
- But you do not necessarily have to do this – the study may not change what you plan to do for the person.
- [pathlabgeorgia.com]

# Sub-types of diabetic neuropathy:
# Treatment Induced Neuropathy of Diabetes (aka Insulin Neuritis)

- This is a very painful neuropathy in distal limbs, axonal and small fiber (sometimes with autonomic findings)
- A drop of over 2-A1c points over three months with onset of symptoms with 3 weeks.
  - 2-3 point A1c drop over 3 months had a 20% risk
  - 4 point A1c drop over 4 months had an 80% risk
- This is difficult to treat and often requires pain medications medications -- a reasonable thought is to reduce A1c to less than 2 A1c points per three months.
- Done at a Tertiary Center (104 pts of 954 met criteria), so these may be sicker than the usual customer. [Gibbons CH, 2015 Brain 138(1): 43-52]



# Sub-types of diabetic neuropathy: Diabetic Lumbosacral Radiculoplexus Neuropathy (aka Diabetic Amyotrophy)

- This occurs in type 2 diabetics, mean age 65, with reasonable glycemic control.
- Involves plexus and roots: usually affects the femoral nerve, may affect sciatic.
- Usually affects one leg, begins with pain (62%), pain may improve, then weakness and numbness in the distribution of the affected nerve.
  - 33 patients, 48% required wheelchair, but at 2 years only 9% needed wheelchair
- The pathology appears to be a microscopic vasculitis
- Several immunotherapies have been tried, all small scale – IV Steroids, Plasma Exchange, ivIGG. Per Cochrane, there is not clear support of these therapies.
- PJ Dyck Neurology 1999; 53(9): 2213-21; PJ Dyck Muscle & Nerve, 2002; 25:477; Cochrane Database Syst Rev 2017(7) CD006521

# Toxin related neuropathies

- Alcohol related neuropathies [Chopra K Br J Clin Pharmacol 2012; 73(3): 348-62]
  - Axonal length dependent neuropathy
  - Often painful, burning pain, allodynia
  - 25-66% of chronic alcoholics may have this, women more than men
  - Likely multifactorial, not just thiamine – malnutrition, toxic effect of alcohol and metabolites
  - Predictable treatment: abstinence, better diet
- Also: Amiodarone (long term), and Diphtheria
- Cancer Related related neuropathies [too large a topic for this talk]
  - 2014 Meta-analysis 4000 pts with neuropathy symptoms at 1 month 68%, at 3 month 60%, and at 6 months 30% -- so this sometimes improves [Seretny M Pain 2014; 5(4):285-96]
  - Common Agents: vinka alkaloids (Vincristine), platinum analouges (Cisplatin), taxanes (Paclitaxel) – but many others list neuropathy as a side effect.
  - Radiation Treatment, commonly for breast cancer can affect the brachial plexus. A brachial plexopathy may show up much later after the treatment has been done.

# A brief note on compressive mono-neuropathies

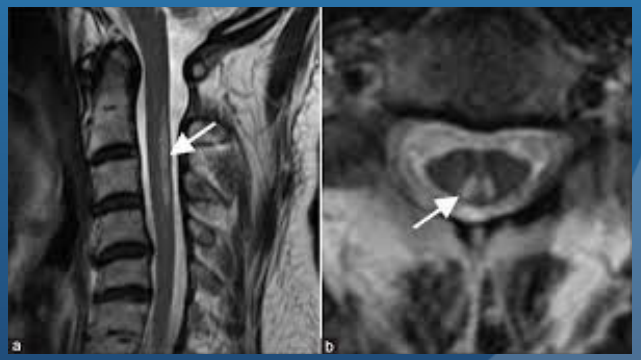
- Carpal tunnel syndrome (median neuropathy at the wrist)
  - An uncomfortable numbness, worse in morning or at night
  - Shakes out the hand, often bilateral
  - No severe weakness, sometimes trouble opening jars
  - Books say digits 1-3 are numb, but people often just say whole hand is numb
- Ulnar neuropathy at elbow
  - They will report numbness in digit 5 and medial edge of digit 4
  - Weakness for finger abduction and grip
- Peroneal neuropathy at fibular head
  - Often a foot drop, and also weakness for foot eversion
  - DDx is L5 radiculopathy, less likely sciatic neuropathy or lumbosacral plexopathy

# B12 Neuropathy

- B12 deficiency
  - Sensory neuropathy in feet, often also in hands (which suggests B12
  - Affects dorsal columns of spine (sensory for position) – also an ataxia
  - Affects corticospinal tract (upper motor neuron signs):
    - Sometimes brisk reflexes and a Babinski reflex (upgoing toes)
    - Sometimes presents with absent ankle reflex, and a Babinski sign
- Check for this with B12 and Methylmalonic Acid (MMA elevated shows low B12).

# B12 Neuropathy

- We often see this with recreational Nitrous Oxide use.
- Other risks:
  - Extended use of Proton Pump Inhibitors, possibly Metformin
  - Gastric bypass, surgical resection of ileum
  - Crohns Disease
- Also, elevated B6:
  - If people take too many B-vitamins
  - Elevated B6 can cause a sensory neuropathy
  - [Sen A, Ann Ind Acad Neur, 2013 16:2):255-258]



# Guillain Barre Syndrome and variants

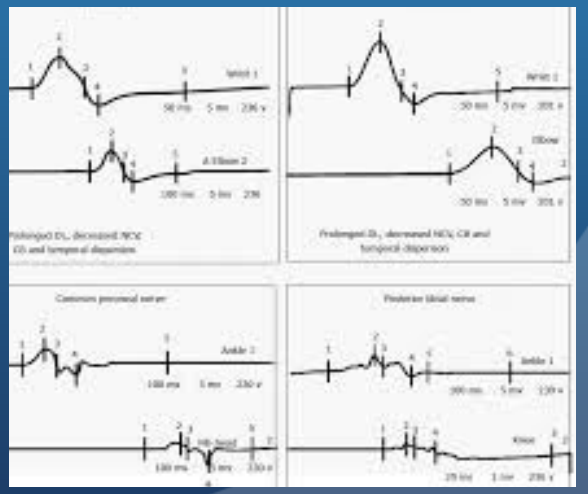
- This is a syndrome, with a classic case but other variants
  - Numbness in feet-legs, then hands
  - Weakness can progress rapidly over days, by defn it should peak before 4 week
  - Areflexia or reduced reflexes
  - About 50% develop facial weakness
- The key tests may be not abnormal at the beginning
  - Spinal Fluid:  elevated protein without abnormal cell – but this may not occur for some days.
  - The EMG-NCS may not be abnormal for three week (F-waves may go first)
- I usually treat this clinically based on the history and exam

# So, I get a call from the ER

- ER doc says I have a person with 36 hours of advancing numbness feet to thighs and hands and some weakness.
- And I ask this question: how are the reflexes?  If the ER doc gets reflexes easily.
- Then I suggest getting a MRI-C Spine, because an advancing cord compression can look just like this.

# For EMG-NCS in GBS

- Once abnormal, common findings include (though it may take 6 weeks):
  - Motor Velocities (two nerves) < 80% LLN, or < 70% if motor amplitude < 80% LLN
  - Partial Conduction Block in one or more motor nerves
  - Motor NCS (2 nerves) distal latency delay > 125% ULN, or > 150% ULN if Amp < 80 LLN
  - F-Waves (2 nerves), > 120% ULN or > 150% ULN if Amp < 80% LLN
- Some sensory nerves may be abnormal, but often the sural sensory nerve (at the ankle) is spared, called “sural sparing”.




- Gorson KC, Ther Adv Neurol Disord 2012; 5(6): 359-373
- Nayak R World J Clin Cases 2017; 5(7)L 270-9

# Variants and Cousins of GBS

- Miller Fisher Syndrome – GQ1b Ab
  - Ophthalmoplegia (diplopia), areflexia, ataxia
  - Often has other Cranial Nerve palsies (often facial paralysis)
- Axonal GBS: AMAN (acute motor axonal neuropathy) – GD1a Ab
  - Common in Northern China, often young people
  - Purely motor, reasonable prognosis
  - Same treatment plan as GBS
- Axonal GBS: AMSAN (acute motor sensory axonal neuropathy)
  - Not associated with GD1a
  - Older population
  - Motor and sensory clinical and on EMG-NCS
  - Worse prognosis

[Griffin JW, Ann Neurol 1996; 39:17-28]

# Treatment of GBS

- Treatment:
  - ivIGG (2gm/kg) over 2-5 days;  or
  - Plasma Exchange (every other day) usually 6 cycles
- Per original data, ivIGG takes some weeks to work, but we have often seen it work quickly.
- There is no data for a second round of ivIGG or adding Plasma Exchange to ivIGG.  But we sometimes do it anyway.

- [Willison JH Lancet 2016; 388-717-27;  van den Berg B Nat Rev Neurol, 2014; 10(8): 469-82; Gonzalez-Suarez I, BMC Neurol 2013; 13:95; Hughes RA, Ther Apher 1997; 1(2):129-30]

# CIDP (chronic inflammatory demyelinating polyneuropathy)

- Similar exam and criteria as GBS (AIDP), but it progresses over 8+ weeks.
  - Similar EMG-NCS Criteria
  - Also elevated Spinal Fluid Protein without significant cells
- ICE Protocol for ivIGG
  - 2gm/kg over 2-5 days
  - Then 1 gm/kg every 3 weeks for 8 cycles (or 6 months) [Hughes RA, Lanc N 2008; 7:2):136-44]
- Can also be treated with:
  - Plasma Exchange
  - Prednisone ( -- I really do not like to give long term Prednisone)
  - Predictable other options: Azathioprine, Mycophenolate, Cyclosporin, Cyclophosphamide
  - When in trouble, we often consider Rituximab
  - [Gorson KC, Ther Adv Neurol Disord 2012; 5(6):359-373]

# Variants of CIDP

- MADSAM (multifocal acquired demyelinating sensory and motor neuropathy)
  - Similar to CIDP but asymmetric and unaffected nerves are normal
  - Treat with same protocol as CIDP
- DADS and anti-MAG Neuropathy
  - Sensory symptoms, sensory ataxia, mild weakness
  - NCS shows VERY delayed distal motor latencies, milder proximal demyelination
  - 2/3 have IgM gammopathies – and with IgM many have anti-MAG Ab
  - Anti-MAG Neuropathies have no real treatment
  - If not anti-MAG, treat as for CIDP, eg ivIGG
- MMN (mulifocal motor neuropathy)
  - Purely motor, presents as multifocal mono-neuropathies, anti-GM1 Ab
  - Very treatable with ivIGG
- POEMS: lambda light chains, neuropathy similar to CIDP
- [Lewis RA, Neurology 1982; 32(9):958-64;  Griffin JW, Ann Neurol, 1996; 39:17-28]

# Para-proteinemia neuropathies

- Monoclonal Proteins
  - About 3-4% of people older age 50, and about 6% over age 75
  - Most are IgG
  - But IgM gammopathies are more likely to cause a neuropathy (about 31% over time had some time of neuropathy)
  - All gammopathies carry a risk of AL Amyloid
  - IgM more of a risk for Waldenstroms
  - Non-IgM more of a risk for Multiple Myeloma
  - Elevated lambda light chains more of a risk for POEMS
- I usually refer this to a Hematologist-Oncologist for an evaluation

- [Chaudhry HM, Mayo Clinic Proc 2017; 92(5):838-50; Nobile-Orazio E, Acta Neur Scand, 1992; 85(6):383-90]

# Paraprotenemia Neuropathies

- IgM-MGUS (often IgM-kappa)
  - Often demyelination
  - Especially DADS and anti-MAG neuropathy
- Waldenstrom (often IgM-kappa)
  - Demyelinating, often sensory ataxia
- AL Amyloid – axonal, small fiber, autonomic, sensorimotor
- Multiple Myeloma
  - Radiculopathy in T-Spine or L-Spine from plasmacytoma or collapsed bone
  - Peripheral Neuropathy is usually later, often related to amyloid
- POEMS (lambda light chains)
  - Demyelination, looks like CIDP
  - VEGF (vascular endothelial growth factor), sens 68%, spec 95%
- [D'Souza A, Blood 2011; 118(7):4663-65]

# Mono-neuritis Multiplex

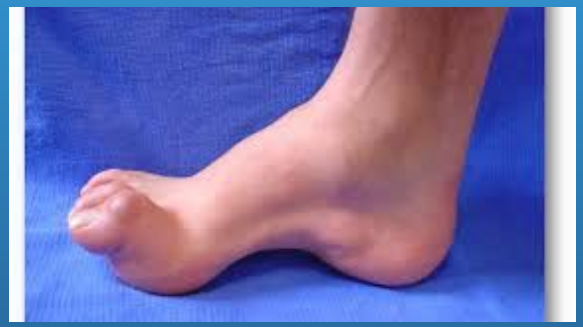
- This is a specific pattern of individual peripheral nerves being affected.
  - Often asymmetric
  - EMG-NCS useful: it can help determine if some nerves are normal and some are badly affected
- Causes
  - Vasculitis
  - Leprosy (becoming less common, I have not personally seen a case)
  - MMN (multifocal motor neuropathy)
    - Purely motor
    - EMG-NCS will show normal sensory and motor conduction block
    - Positive for anti-GM1 Ab, treatable with ivIGG

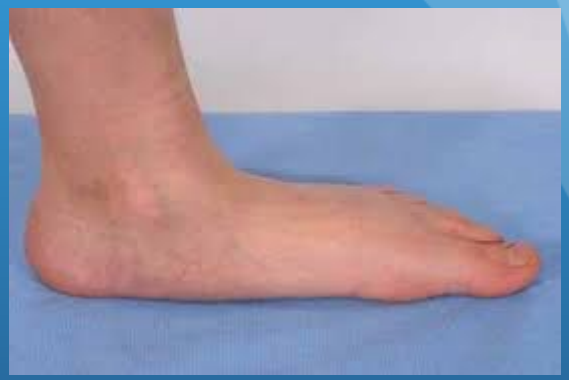
# Vasculitic Causes of Mono-neuritis Multiplex

- Primary Vasculitis
  - Microscopic polyangitis (small vessel)
  - Churg-Strauss (asthma, eosinophlia, small vessel)
  - Wegener's with polyangitis (small vessel)
  - Polyarteritis nodosa (medium vessel)
- Secondary Vasculitis
  - SLE, RA, Sjogren's, Sarcoid, Behcets
  - Paraneoplastic:  anti-Hu, Yi, Ri, CRMP-5
- Comment: if it affects the voice, they sometimes think it is ALS
- This is one of the rare cases where we move to nerve and muscle biopsies

# Inherited Neuropathies: Charcot Marie Tooth

- Charcot Marie Tooth
  - A clinical diagnosis, done pre-DNA era with family tree histories.
  - Dysmyelinating, slow nerve conductions, often motor velocity < 25 m/s





- [nasiruddinsnc.wordpress.com; ghr.nlm.nih.gov; KU Medical Center Grounds Rounds, Karthika Veerapanemi, MD 2016]

# Charcot Marie Tooth – lots of genes

- CMT1 – Autosomal Dominant, dys-myelinating, the classic form
  - CMT1A is the most common, PMP-22 gene
  - Also 1B, 1C, 1D, 1E, 1F
- CMT2 – Autosomal Dominant, but axonal (13 genes)
- CMTX – X-linked, CMTX1 is the second most common after CMT1A
- CMT3 – Dejerine-Sottas, severe in infancy, Motor < 10 m/s
  - Autosomal Dominant (PMP22, also MPZ, EGR2), Autosomal Recessive (PRX)
- CMT4 – Autosomal Recessive, dys-myelinating, rare
- HNPP – hereditary neuropathy to pressure palsies
  - Also PMP-22 gene, but a different deletion
  - Prone to CTS, ulnar neuropathies, but can be healthy
- There are several companies which can do a complete inheritance panel, some for as little as $250 dollars.

# FDA Approved Drugs for Neuropathic Pain

- Gabapentin (post-herpetic neuralgia)
- Pregabalin (diabetic neuropathy)
- Duloxetine (diabetic neuropathy)
- Lamotrigine (post-herpetic neuralgia)
- Carbamazepine (trigeminal neuralgia)
- Tricyclics (for chronic pain)
- Opioid Analgesics and Tramadol (pain in general)

# Statins and Neuropathy

- People will Google and association with Neuropathy and Statins, the data is not especially compelling.
- 2002: 166 cases of neuropathy (35 definite, 54 probable, 77 possible), retrospective via a prescription register: assessed odds-ratio 0f 3.7 total, 14.2 for definite [Gaist D Neurology, 2002, 58:1333-7]
- 2019: 333 with unexplained axonal neuropathy versus 283 healthy controls, showed no difference in statin use (but done in Holland). [Warendorf JK, Neurology 2019, 92: e2136-44]

# When to send stuff to us

- Well, you can send us anything (. . . neurology is the home of the unexplained symptom)
- But especially if it is:
  - If it is rapid
  - If it is motor
  - If it is un-explainable
  - And we often repeat the EMG-NCS (I like to see my own)
- Use the labs and EMG-NCS studies, but be aware of the limits on them

# To Repeat: a good lab workup

- Glucose
  - If glucose normal, add a glucose challenge test (2 hour) and-or A1c
- Renal Panel
- CBC
- ESR
- B12 and also Methylmalonic Acid (increases sensitivity)
- B6 (excess B6 can cause a neuropathy) and occasionally B1
- TSH
- Para-proteinemias:
  - Serum Protein Electrophoresis (SPEP)
  - AND ALSO: Serum Immunofixation (SPEP alone may miss 30% of IgM Monoclonal Ab, which are more prevalent in neuropathy.
- If there is a Risk: HIV, Lyme (prefer Western Blot)
- If a strong family history: the genetic panels have become less expensive (usually private labs)

# Thank you