Normal Saltatory Conduction

Kindly provided by Michael Rasminsky from his work done with Tom Sears and Hugh Bostock
Based on recordings from mice at successive sites 200 microns apart.

Membrane currents determined by subtracting adjacent external longitudinal currents.
What We’ll Do

- Will present 2 cases to illustrate some clinical and physiologic points
- Will leave time for discussion and questions about problems that you might encounter
1990–28 year old woman presented with right foot drop that came on acutely
Numbness in lateral calf
Exam – Common peroneal neuropathy
EMG– Conduction block at knee
Other conduction changes
  ◦ Prolonged median, peroneal (bilat) distal latencies;
  ◦ Slowing of ulnar conduction across the elbow without block
  ◦ Slowing of left peroneal conduction across the knee.
Diagnosed as L-SS
Received course of steroids and symptoms and signs improve
Dr. Lewis leaves town!
1 year later she has right radial palsy and sees my ex-partner
EMG similar but PMCB of radial nerve
Nerve biopsy
Tomaculae

- Pathologic Hallmark of HNPP
What I Learned

- Original description of L-SS was of conduction block *not* at sites of compression
  - Read your own articles
- Many patients with inherited neuropathy have no family history
  - De novo mutations
  - Variable expression
  - Recessive cases
- Don’t leave your patients to partners who are smarter than you
Hereditary Neuropathy with Liability to Pressure Palsies

- Multifocal neuropathy with symptoms due to compression
- Symptoms persist for days or weeks
- PMP–22 deletion or mutation that causes functional deletion
- Because conduction changes may be seen in asymptomatic regions – can be confusing to electromyographer
Electrophysiology of HNPP

- The chronic disorder
  - What are the electrodiagnostic findings in patients in between attacks?

- The acute condition
  - What is known about the electrophysiology of the acute lesion?
  - How does it compare to acute nerve palsies in non-HNPP patients?
Distal Motor Latencies in HNPP

- Median > Ulnar
- Peroneal
- Tibial Normal

Li J, Krajewski K, Shy ME, Lewis RA. Neurology 58:1769–73; 2002
Conduction Abnormalities Predict HNPP

- Distal slowing
  - Median > Peroneal > Ulnar > Tibial
  - Terminal Latency Index
- Ulnar slowing across Elbow – 100%
- Peroneal slow across knee – 85%
- Sensory amplitudes reduced and latency prolonged
HNPP: Progressive Axonal Loss

- Studies of multiple families have shown that CMAP amplitudes are lower in older patients with HNPP.
- A few longitudinal studies have also shown progressive axonal loss with age.
- This points to HNPP as not only a disorder of episodes of compression but also as a progressive neuropathy.
The Acute Nerve Palsy in HNPP

- Conduction block
- Can persist for years but usually resolves over weeks to months
- What makes the nerves liable to pressure?
- Is the acute palsy in HNPP different than in normals?
Acute Compressive Neuropathy

- Prolonged block due to compression not ischemia
- Block caused by pressure differential - invagination of nodes
- Recovers in 3-4 months

Conduction Block is Always Reversible?
Block occurs before demyelination
Demyelination develops later
Block persists until remyelination
HNPP MICE HAVE AXONAL CONSTRICITION and THINNING AT TOMACULAE

Axonal Stretching and Thinning in Non-Compressed Nerves
CMAP amplitude declines with age

A

Rotarod Test

B

Fibers/mm²

C

Time (sec)

WT HKO 1m

WT HKO 2m

WT HKO 3m

pmp22 +/-
Conclusions from HNPP Mice Study

- PMP–22 deficiency induces more rapid and longer lasting block
  - Also seen in MAG–/– mice but not MPZ deficient mice
- PMP22 protects against nerve injury
- Axonal constrictions may induce susceptibility to block
  - Increased axonal resistance
- Compression also causes axonal stretching and thinning
- Nodal invagination (as seen by Gilliatt, Ochoa et al) rarely seen
  - Probably only seen in severe compression
- Effects on axon may produce chronic length–dependent axonal loss
HNPP: New Concepts

- There is a characteristic pattern of changes in chronic patients even when asymptomatic.
- Conduction block may be occurring due to changes at the Node of Ranvier due to effects of tomaculae.
- Progressive length-dependent axonal loss is related to the chronic effects of axonal constriction of the axon from the tomaculae.
Case 2: Last Week

- 63 year old man from California was seen for a 3rd opinion. Current diagnosis of MMN
- 12 years ago developed right shoulder weakness after playing in volleyball tournament. Improved 70% over 3–4 months with therapy.
- 7 years ago shoulder weakness returns and develops further weakness of right arm and hand which has gradually progressed to virtually flail limb
2008 – Unable to write with right hand
  ◦ 1st rib resection for TOS – no improvement
2010– Foot dorsiflexion weakness recognized
Jan 2011– 8 weeks of IVIg without change
July 2011– Right arm without function
  ◦ Bilateral foot weakness
No family history
No other medical issues
EMG in CA shows bilateral ulnar conduction blocks
Case 2 Exam

- Abnormal nystagmoid eye movements
- No facial, tongue, palate or SCM/Trapezius weakness
- Right arm– Delt 2/5 Others no better or worse
  - Rhomboids and serratus appear normal
- Left arm– intrinsics 4/5 Others 5/5
- Legs– Foot dorsis 3/5
  - Plantar flex 4+/5
  - Toe dorsiflex 3/5
DTRs
- Right arm = 0/5  Left arm = 2+
- Legs 2+ knees and 1+ ankles

Sensory
- Right arm—reduced vibration, position, pin
- Left arm—Vibration decreased but position OK
- Legs—Decreased in feet—all modalities
- Abnormalities do not fit specific dermatomal distribution
Clinically – this looked like a distal sensory and motor neuropathy with a superimposed flail arm!

An obvious case of ..... Beats the .... out of me!!
## Nerve Conduction

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Stimulate Record</th>
<th>AMPLITUDE (mV or μV)</th>
<th>LATENCY (ms)</th>
<th>CONDUCTION VELOCITY (m/sec)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>L</td>
<td>Norm</td>
</tr>
<tr>
<td>Median Motor</td>
<td>Wrist APB</td>
<td>2.9</td>
<td>5</td>
<td>(&gt;4)</td>
</tr>
<tr>
<td></td>
<td>Elbow</td>
<td>3.0</td>
<td>5</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>Axilla</td>
<td>2.8</td>
<td>6</td>
<td>9.5</td>
</tr>
<tr>
<td>Median F-Resp</td>
<td>Wrist Thenar</td>
<td>39.5</td>
<td>29.3</td>
<td>(&lt;31)</td>
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<tr>
<td>Ulnar Motor</td>
<td>Wrist Hypoten</td>
<td>2.8</td>
<td>7</td>
<td>(&gt;6)</td>
</tr>
<tr>
<td></td>
<td>B Elbow</td>
<td>0.1</td>
<td>3</td>
<td>9.7</td>
</tr>
<tr>
<td></td>
<td>A Elbow</td>
<td>0.1</td>
<td>3</td>
<td>11.2</td>
</tr>
<tr>
<td></td>
<td>Axilla</td>
<td>0.1</td>
<td>3</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td>Erbs</td>
<td>1.3</td>
<td>1</td>
<td>9.7</td>
</tr>
<tr>
<td>Ulnar F-Resp</td>
<td>Wrist Hypoten</td>
<td>35.0</td>
<td>32</td>
<td>(&lt;32)</td>
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<tr>
<td>Median Sensory</td>
<td>Wrist Index</td>
<td>0.8</td>
<td>2</td>
<td>(&gt;25)</td>
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<tr>
<td>Ulnar Sensory</td>
<td>Wrist 5th</td>
<td>nr</td>
<td>1</td>
<td>(&gt;10)</td>
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<tr>
<td>Radial Sensory</td>
<td>Forearm Wrist</td>
<td>nr</td>
<td>2</td>
<td>(&gt;14)</td>
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<tr>
<td>Peroneal Motor</td>
<td>Ankle EDB</td>
<td>nr</td>
<td>(&gt;3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B Knee</td>
<td>nr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peroneal Motor</td>
<td>Fib Head Ant Tib</td>
<td>1</td>
<td>(&gt;4)</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>A Knee</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sural Sensory</td>
<td>Calf Ankle</td>
<td>nr</td>
<td>(&gt;6)</td>
<td></td>
</tr>
</tbody>
</table>

### Electromyography

**N** = normal, **unsust** = unsustained

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Insertional/Spontaneous</th>
<th>Volunt Motor Unit Potential</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ins p wave</td>
<td>fasc</td>
</tr>
<tr>
<td>R-FDI (Hand)</td>
<td>N</td>
<td>unsust</td>
</tr>
<tr>
<td>L-FDI (Hand)</td>
<td>N</td>
<td>0</td>
</tr>
<tr>
<td>L-Abd Dig Quinti (Hand)</td>
<td>N</td>
<td>0</td>
</tr>
<tr>
<td>L-Extensor Indices</td>
<td>N</td>
<td>0</td>
</tr>
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</table>
Findings and Interpretation

- All sensory responses were absent or severely reduced
- Motor responses absent distally and reduced in amplitude in anterior tibialis without conduction velocity or latency abnormality
- Right median motor amplitude reduced
- Bilateral ulnar conduction blocks in the forearm!!
- Is this a form of CIDP??
Left Ulnar Motor Nerve Conduction
Left Ulnar Motor Conduction Study to ADM with Inching of Median from Forearm to Elbow
Right Ulnar Motor Conduction to ADM
Martin–Gruber Anastomosis
Detection of Conduction Block and the Pitfalls
Normal Saltatory Conduction

Kindly provided by Michael Rasminsky from his work done with Tom Sears and Hugh Bostock
How Does One Determine Conduction Block?

- Remember that you’re assessing many fibers not single nerve fiber physiology
- Clinically we look at amplitude drop which tells us whether the same nerve fibers are stimulated proximally as distally
- Criteria vary from 20% reduction to 50%
  - Specific or sensitive??
  - 20% is reasonable only for short segments but not always easy to stimulate in short segments
  - 50% specific but miss mild block
Recording from patient with MMN showing motor but not sensory block
Clinical Electrodiagnostic Consequences of Demyelination

Richard A. Lewis, MD
Professor and Associate Chair of Neurology
Wayne State University School of Medicine
Detroit, MI
Mistakes in Assessing Conduction Block

- Submaximal Stimulation proximally
- Excessive stimulation distally
- Not taking into account Martin–Gruber Anastamoses
- Not taking distance into account
- Not correlating with clinical exam
Pitfalls in Determining Conduction Block

- The longer the nerve segment the more normal temporal dispersion and phase cancellation
  - Tibial nerve confuses
  - Beware of basketball players
- Marked axonal loss may allow excessive temporal dispersion and confuse
Pseudo-Conduction Block

- **Sub-maximal stimulation proximally**
  - Tibial at Popliteal Fossa
  - Erb’s Point
- **Over stimulation distally**
  - Median nerve at the wrist

Always make sure that the distal CMAP is consistent with clinical strength and bulk. Make sure the degree of block fits the clinical picture. Check EMG for motor unit recruitment.
Electrodiagnostic Findings That Suggest Demyelination

- Conduction Block
- Conduction Slowing
- Segmental Slowing
- Temporal Dispersion
- Distal Accentuated Slowing
- Distal Duration Prolongation
Changes in Chronic Demyelinating Neuropathies

- Conduction Block important in acute disorders but also seen in chronic neuropathies
- Persistence of block in Lewis–Sumner and MMN and a few cases of HNPP
  - Some evidence from axonal excitability studies that focal and lasting axonal hyperpolarization seen in MMN
- Temporal Dispersion, Conduction Slowing more critical issue in chronic disorders
Demyelinating Abnormalities

- Conduction velocity < 70% of LLN
  - Arms < 35 m/sec
  - Legs < 28 m/sec
- Segmental slowing
  - DML slowing when velocity normal (TLI)
  - F wave slowing when velocity normal
- Temporal Dispersion
- Conduction Block
Conduction Velocity is Proportional to Nerve Fiber Diameter

Smallest diameter motor nerve fiber (5-6μm) distally in legs may conduct between 25 and 30 m/sec.

In arms smallest motor fiber (6-7 μm) cannot conduct below 30 m/sec.
Demyelination is inferred when the conduction velocity is slower than can be accounted for by axonal loss

In the arm—no normal motor axon can conduct at less than 30 m/sec
  ◦ Any median or ulnar conduction below 30 m/sec by definition is a sign of demyelination

When amplitudes are reduced and velocities are near normal (>42 m/sec?) then the primary process is axonal
But How Does One Interpret Intermediate Changes?

- Compare amplitude to velocity
- Is slowing is out of proportion to amplitude
  - CV of 38 m/sec with Normal Amp. = demyelinating neuropathy
  - CV of 38 m/sec with amp < 20% of normal may be axonal
- Look for temporal dispersion, conduction block, multi-focal changes
Conduction slowing that occurs variably along the length of the nerve must be due to segmental demyelination.

Slowing in axonal neuropathies is uniform.

Remember that proximal segments are normally faster than distal segments due to tapering.
Temporal Dispersion

- Prolonged duration of CMAP suggests excessive slowing of intermediate conducting nerve fibers.
- Usually discussed when comparing CMAP on proximal stim compared to distal
- Distal CMAP dispersion now being used as criteria for demyelination (> 9 msec)
Not All Temporal Dispersion is the Same

- Normal dispersion related to length of nerve
- Uniform slowing causes greater dispersion but all fibers affected similarly
- Non-uniform, CMAP breaks up with variable slowing of different fibers.
Temporal Dispersion: Uniform or Multifocal

- When CMAP duration widens uniformly all the motor fibers are slowing equally
- When the CMAP breaks up it suggests differential slowing of fibers—multifocal slowing
Thanks for Listening
Intraneural injection of sera from GBS pts or from rabbits with EAN and anti–GalC produced block starting within 30 minutes.

Conduction Block can occur without internodal demyelination or Na⁺ Channel Block
Conduction Block = Demyelination?

Mechanisms of Conduction Block

† Na Channel Block
  ◦ Local Anesthetics; Toxins such as Tetrodotoxin (puffer fish); GBS (AMAN); MMN?

† Demyelination – Acute
  ◦ GBS (AIDP); MMN ?; L–SS; Acute Compression; MS

† Depolarization
  ◦ Nerve Ischemia

† Hyperpolarization
  ◦ Activity dependent; post–ischemia
Conduction Block Without Demyelination: AMAN

- Unique Immunologic disorder with block but no subsequent demyelination
- Recovery or axonal degeneration
Left Median Motor Nerve Conduction

Patient: Smith
Birth Date: 5/10/1940
Age: 79 y
Gender: Male
Technician: Karen

Stim Phys.: Dr. Lewis
Ref Dr.: Dr. Fax

Repeating Sites:

<table>
<thead>
<tr>
<th>Stimulus Site</th>
<th>Distance (mm)</th>
<th>Lat. Onset</th>
<th>Amp. B-P</th>
<th>C.V.</th>
<th>Area B-P (mVms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Wrist</td>
<td>70</td>
<td>4.3 ms</td>
<td>6.4 mV</td>
<td>n/a</td>
<td>16.3</td>
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<tr>
<td>2 Elbow</td>
<td>200</td>
<td>10.8 ms</td>
<td>6.1 mV</td>
<td>44.8</td>
<td>17.2</td>
</tr>
<tr>
<td>3 Axilla</td>
<td>100</td>
<td>12.3 ms</td>
<td>8.0 mV</td>
<td>66.7</td>
<td>20.8</td>
</tr>
<tr>
<td>4 Site 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Site 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Site 6</td>
<td></td>
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</tr>
</tbody>
</table>

C.V. Calculation

Temperature: **°C**

APS Segmental

Wrist: 5.0 mV / 2.0 ms; Stim 37.3 mV, 0.1 ms
Elbow: 5.0 mV / 2.0 ms; Stim 64.4 ms, 0.2 ms
Axilla: 5.0 mV / 2.0 ms; Stim 100 mV, 0.2 ms

XLTEK
Uniform vs Non–Uniform Conduction Slowing in Inherited Neuropathies

**Uniform**
- CMT–1A
- CMT–1B ??
- ?CMT–1C (SIMPLE)
- Dejerine–Sottas
- Leukodystrophies
- Metachromatic
- Cockayne’s
- Krabbe’s

**Non–Uniform**
- HNPP
- Some CMT–1B?
- CMTX
- Adrenomyeloneuropathy
- Pelizeus–Merzbacher
- Refsum’s
- Adult Krabbe’s
Distinction Between CIDP and CMT: No Longer So Simple

- Non-uniform slowing suggests acquired disorder?
- Adult onset CMT–1B
- CMT–X women can present later in life without family diagnosis
  - Case of 76 yo (Tabaraud et al M&N 1999)
- Demyelinating neuropathy without family history
- CIDP may occur in someone with CMT
  - (Ginsberg et al Brain 2004)
- Steroid responsive CMT
Disclosures

- Consult for CSL Behring, Baxter in developing clinical trials for CIDP
- Consult for BMS in reviewing potential neuromuscular complications of new anticoagulant
- No conflicts related to this presentation
- Gamunex brand of IVIg is approved for treatment of CIDP. All other discussions of treatments for the inflammatory neuropathies would be “off label”