Navigating the Seas Between Diabetic and Inflammatory Neuropathies

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DISCLOSURES

Consultant: CSL Behring; Pharnext; Argenx; Akcea; Annexon; Biotest; Annexon; Seattle Scientific

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Board of Directors: Peripheral Nerve Society (President-Elect)

Medical Advisory Boards: GBS-CIDP FI; MGFA; MGF of California; Foundation for Peripheral Neuropathy
What We’ll Talk About

• The Spectrum of Diabetic Neuropathy
  • The Spectrum of CIDP
• The Overlap of Diabetic Neuropathy and CIDP
• The Problems in Diagnosing CIDP in Diabetics
  • An Approach to Navigate the Seas
# The Spectrum of Diabetic Neuropathies

<table>
<thead>
<tr>
<th>Symmetric</th>
<th>Focal/Multifocal</th>
</tr>
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<tbody>
<tr>
<td>• Distal Sensorimotor Polyneuropathy</td>
<td>• Diabetic Radiculoplexopathy (Amyotrophy)</td>
</tr>
<tr>
<td>• Distal Sensory Large Fiber Neuropathy</td>
<td>• Thoracic Radiculopathy</td>
</tr>
<tr>
<td>• Distal Small Fiber Neuropathy</td>
<td>• Cranial Mononeuropathies</td>
</tr>
<tr>
<td>• Diabetic Autonomic Neuropathy</td>
<td>o Diabetic pupillary sparing 3(^{rd}) Nerve Palsy</td>
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<tr>
<td></td>
<td>• Compressive Neuropathies</td>
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# Diabetes and CIDP: Where They Get Confused

<table>
<thead>
<tr>
<th><strong>DIABETES</strong></th>
<th><strong>CIDP</strong></th>
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</thead>
<tbody>
<tr>
<td>• Distal Sensori(motor) Neuropathy</td>
<td>• DADS: Distal Acquired Demyelinating Sensori(motor) Neuropathy</td>
</tr>
<tr>
<td>• Diabetic Small Fiber Neuropathy</td>
<td>• Sensory CIDP</td>
</tr>
<tr>
<td>• Diabetic Radiculoplexopathy</td>
<td>• Immune SFN: What’s the Evidence?</td>
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<td></td>
<td>• Lewis-Sumner Syndrome</td>
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</tbody>
</table>
Distal Symmetric Large Fiber Neuropathy: Clinical Features

• Sensory Predominant
  o Symptoms of paresthesias, numbness; “walking on rocks”; Feet feel tight
  o Worse at night
  o May be asymptomatic- detected on exam
  o Slow and insidious progression

• Length Dependent
  • Reduced or absent ankle reflexes but others preserved
  • Vibration reduction- earliest feature
  • Motor involvement later and mild- can detect changes in foot muscles earlier but not symptomatic
Distal Symmetric Large Fiber Neuropathy: Electrodiagnostic Features

- Reduced Sural Sensory Amplitudes
  - If normal, check medial plantar responses
- Motor studies may be normal or
  - Reduced EDB amplitudes
  - Prolonged F wave latencies (Yes- even with axonal neuropathies)
- May have conduction slowing at sites of compression (with or without symptoms)
Diabetic Small Fiber Neuropathy

- Characterized by burning pain in feet
- Normal ankle reflexes and vibration sense
- Pin and temperature sense abnormalities is variable
  - How do you test temperature?
- No weakness or atrophy
- Normal Nerve Conduction Studies
- Abnormal intraepidermal nerve fiber density on skin biopsy
  - Typically in length dependent fashion
  - Caution: Variable results from different labs
  - Is a reduction of 1 nerve fiber/mm clinically meaningful?
Most Symmetric Diabetic Neuropathies Are A Combination of Large and Small Fiber
RED FLAGS IN DISTAL SYMMETRIC NEUROPATHY: Consider Other Disorders

- Weakness out of proportion to sensory loss
  - Foot drops are unusual unless severe and usually diabetes poorly controlled
    - Proximal weakness should not be present
- Generalized areflexia
- Aggressive progression
CIDP and IgG and IgA MGUS
CIDP and IgM MGUS
Anti-MAG
MMN
CIDP plus systemic disease
Diabetic Neuropathies?
CIDP plus CNS Demyelination
Chronic Acquired Demyelinating Neuropathies
Diabetic Neuropathies?
Sensory variants
CANOMAD
Anti-GD1B
Ataxia with Anti-GM2 and GD1A
CIDP
CISP
MMN
Lewis-Sumner
Nodo/Paranodopathies
Neurofascin 155
Contactin 1
Chronic Immune Mediated Demyelinating Neuropathies
Chronic Immune Mediated Demyelinating Neuropathy (CIMDP)

- CIDP
  - Classic
  - Variants
- Not-CIDP
  - Paraprotein related
  - Strong Association
    - IgM
    - POEMS
  - Weak Association
    - IgG
    - IgA

CIDP Variants

- Distal (DADS)
- Pure Sensory
  - CISP?
- Multifocal
  - Lewis-Sumner
- Nodo/Paranodopathies?
  - Neurofascin 155
  - Contactin 1
  - CASPR; Neurofascin 186?
Chronic Inflammatory Demyelinating Polyneuropathy

• “Typical or Classic Features”
  o Progression over 2 months
  o Symmetric
    o Proximal and distal muscles
  o Motor > sensory
  o Absent or reduced reflexes
  o Increased CSF protein
  o Demyelination on NCV and/or biopsy
59 patients referred to Dr. Allen at NWU with the diagnosis of CIDP

Records reviewed and full clinical assessment and EMG

Blinded case review by RAL

JA- RAL concurrence in 58/59 cases

EFNS/PNS criteria met in 31/58 (53%)
  - Definite (87%), Probable (3%), Possible (10%) requirements.

27/58 (47%) were not considered to have CIDP both by these criteria and by our assessment

Better alternative diagnosis considered
Alternative Diagnoses in 27/58 patients with “non-CIDP”
What Were the Reasons for Misdiagnosis?

• 44% of non-CIDP met clinical criteria but all were “atypical”
• Only 14% of non-CIDP met EMG criteria vs 100% of CIDP
• CSF protein increased in 50% without CIDP but only 10% were > 100 mg% vs 55% of CIDP
• 37% non-CIDP seen by neuromuscular specialist vs 68% with CIDP
Diagnostic Data in CIDP and Not-CIDP Groups

<table>
<thead>
<tr>
<th></th>
<th>Clinical</th>
<th>NCS</th>
<th>CSF</th>
<th>MRI</th>
<th>Biopsy</th>
<th>Improve with IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIDP (N=31)</td>
<td>18 (100%)</td>
<td>17 (94%)</td>
<td>16 (89%)</td>
<td>13 (72%)</td>
<td>3 (17%)</td>
<td>14 (78%)</td>
</tr>
<tr>
<td>Not CIDP (N=28)</td>
<td>7 (37%)</td>
<td>3 (16%)</td>
<td>6 (32%)</td>
<td>1 (5%)</td>
<td>0 (0)</td>
<td>13 (68%)</td>
</tr>
</tbody>
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Improvement was based on **subjective report** by patient

*Objective improvement was seen in only 19% of non-CIDP but 69% of CIDP*
<table>
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<tr>
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<th>CIDP (n = 31)</th>
<th>Not CIDP (n = 27)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at evaluation, y, mean (SD, range)</td>
<td>47.2 (11.6, 20-67)</td>
<td>49.8 (14.2, 25-77)</td>
<td>0.59</td>
</tr>
<tr>
<td>Male, %</td>
<td>61.3</td>
<td>51.9</td>
<td>0.60</td>
</tr>
<tr>
<td>Chicago area residence, %</td>
<td>51.8</td>
<td>45.1</td>
<td>0.79</td>
</tr>
<tr>
<td>Symptom duration, mo, mean (SD, range)</td>
<td>72.3 (75.5, 6-252)</td>
<td>99.4 (72.6, 6-240)</td>
<td>0.16</td>
</tr>
<tr>
<td>Time since diagnosis, mo, mean (SD, range)</td>
<td>60.9 (70.2, 4-216)</td>
<td>36.0 (34.8, 6-120)</td>
<td>0.10</td>
</tr>
<tr>
<td>EFNS/PNS clinical criteria, %</td>
<td>100</td>
<td>44</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EFNS/PNS clinical criteria, typical, %</td>
<td>80.6</td>
<td>0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EFNS/PNS electrodiagnostic criteria, %</td>
<td>100</td>
<td>14.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EFNS/PNS electrodiagnostic criteria, definite, %</td>
<td>84.4</td>
<td>11.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CSF cytoalbuminologic dissociation, % (n)</td>
<td>90.3 (31)</td>
<td>50.0 (20)</td>
<td>0.02</td>
</tr>
<tr>
<td>CSF protein mg/dL, mean (SD, range)</td>
<td>156.3 (130.5, 33-550)</td>
<td>61.4 (30.7, 18-128)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MRI nerve root enhancement/enlargement, % (n)</td>
<td>75 (24)</td>
<td>10.5 (19)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Nerve biopsy demyelination/remyelination, % (n)</td>
<td>50 (6)</td>
<td>0 (7)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Abbreviations: CIDP = chronic inflammatory demyelinating polyneuropathy; EFNS/PNS = European Federation of Neurological Societies/Peripheral Nerve Society.
Nerve Conduction Interpretation Issues

1. Overemphasis of EDB response and not looking at TA
2. Not recognizing the confounding changes from diabetes and compression
3. Not looking at upper extremities
4. Not appreciating the degree of slowing that can occur with axonal loss
KEY ISSUE:
EMG INTERPRETATION
Electrodiagnostic errors contribute to chronic inflammatory demyelinating polyneuropathy misdiagnosis. (Allen JA, Ney J, Lewis RA. Muscle Nerve 2018; 57: 542-549)

• EDX errors contributed to mis-diagnosis in 55%
• Interpretation errors major issue
• Length dependent axonopathies, motor neuron disease and diabetic neuropathies major confusing diagnoses
• Don’t depend on lower extremity nerves alone;
• Do studies to proximal muscles when distal muscles are atrophied
• Be wary in diabetes and any atypical case
Where Were The Problems?

• It wasn’t technical proficiency
  ☐ Although temperature not reported in most
• Comparison of two studies showed minimal differences even though a mean of 31 months separation
  ☐ The disease must not have progressed much or improved much
• It was in the interpretation
What Were the Interpretation Issues?

- The one patient who met EFNS EDX criteria was subsequently found to have SH3TC2 mutation (CMT 4C)
- 21% (6/29) considered abnormal were normal
- 45% (13/29) had length dependent axonopathies
- 21% had motor neuron disorder
- 12% had changes only at sites of compression
Further Identification of Errors in Electrodiagnosis

- All 13 patients with length dependent axonopathies had conduction slowing but all but 2 had amplitude reduction that accounted for the changes or sites of compression
  - 59% of the 29 patients had the major abnormality in the peroneal nerve to the EDB ranging from 28-36 m/sec with amplitudes of 0.1-1 mV
  - Only 5 had proximal studies to TA- none of these were slow
What Did We Learn?

- USE CRITERIA
- BE CAREFUL WITH ATYPICAL CASES
- DON’T DIAGNOSE PURELY ON LOWER EXTREMITY NCS
- SUBJECTIVE TREATMENT RESPONSE IS UNRELIABLE
- USE OBJECTIVE MEASURES TO DETERMINE TREATMENT RESPONSE
- REFER TO NEUROMUSCULAR SPECIALIST
  - GBS-CIDP FI Centers of Excellence
  - Maybe before initial treatment but definitely if no robust objective response
Mis-Diagnosis of CIDP in Diabetics

• The clinical overlap of diabetic neuropathy is with DADS and Sensory variants
• Conduction slowing can be seen in diabetic neuropathy
• Peroneal slowing to the EDB can be misinterpreted
• Temperature of distal regions altered in diabetics
• Conduction slowing at sites of compression can be misinterpreted as due to inflammatory neuropathy
• Diabetics can have CSF protein elevation of 100 mg%
What Do We Know about DADS?

• Distal Acquired Symmetric Demyelinating Neuropathy (DADS) described by Saperstein et al 2000- it’s a phenotype not a disease
• ~50% DADS have paraprotein = DADS-M
  o Most DADS-M IgM kappa and anti-MAG
• DADS (no M) considered to be CIDP variant
• Recent reviews point to significant conduction slowing
• Italian study* of 460 patients with CIDP had 19% atypical cases
  o DADS 7%; Pure Sensory 3.5%; LSS 4%; pure motor 4%
  o DADS and LSS- less responsive to IVIg
  o At onset of symptoms 39% atypical with 13% DADS and 11% sensory (2 with CISP)
  o 53% progressed to typical with mean duration of 5.5 years (1-38). Pure sensory converted in 48% but only 24% of DADS

*Doneddu PE et al. JNNP 2019
## Italian Review of Atypical CIDP
(Donneddu PE et al. JNNP 2019)

<table>
<thead>
<tr>
<th>DADS (N=34)</th>
<th>Sensory (N=16)</th>
<th>Typical (n=376)</th>
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<tbody>
<tr>
<td>• 70% fulfilled EFNS criteria-21 definite; 3 probable</td>
<td>• 75% EFNS</td>
<td>82% EFNS</td>
</tr>
<tr>
<td>• CSF protein increase in 90%. Mean 93 (range 46-193)</td>
<td>• 12 had demyelinating features on motor studies despite pure sensory</td>
<td>86% increased CSF protein; mean 123 (46-1000)</td>
</tr>
<tr>
<td>• 7/34 had increased DML</td>
<td>• CSF protein 67% increased – Mean 86 (46-193)</td>
<td>IRODS 33; INCAT 2.7</td>
</tr>
<tr>
<td>• IRODS 39/48 INCAT 1.5</td>
<td>• IRODS 38; INCAT 1.7</td>
<td>Treatment response 87%; Steroids 51%; IVIg 78%</td>
</tr>
<tr>
<td>• Treatment response 64%; Steroids 56%; IVIg 50% No difference if met EFNS or not</td>
<td>• Treatment response 90%; steroids 67% IVIg 86%</td>
<td></td>
</tr>
</tbody>
</table>
Interpretation of Conduction Abnormalities in Diabetes
EFNS/PNS Guidelines: Electrodiagnostic Criteria

- **Definite:** Clearcut slowing in two nerves
  - DML - 50% prolongation
  - **Conduction Velocity - 70% of LLN**
    - Uppers: $50 \text{ m/sec} \times 0.7 = 35 \text{ m/sec}$
    - Lowers: $40 \text{ m/sec} \times 0.7 = 28 \text{ m/sec}$
  - F wave prolongation - 20% prolongation
  - Conduction Block - 50% drop
  - Distal CMAP duration - $>9 \text{ msec.}$ in one nerve and another abnormality in another nerve

- **Probable:** CB of 30% in one + another abnormal

- **Possible:** Same but only in one nerve
WHERE DO THESE CRITERIA COME FROM?

WERE THESE ARBITRARY LEVELS OR ARE THERE PHYSIOLOGIC PRINCIPLES INVOLVED?
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.
Problems In Interpretation of Nerve Conduction Studies

• 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
  o Any median or ulnar conduction below 30 m/sec by definition is a sign of demyelination/ remyelination
• In the peroneal and tibial- velocities of 28 m/sec could still come from axonal loss
• Be wary of interpretation when amplitudes < 0.5 mV
  o Is your take-off sharp?
• Check conduction to more proximal muscles
  o Peroneal to TA
  o Median/ulnar to forearm
THE SPECIAL PROBLEM IN DIABETES

• Conduction slowing can occur in diabetes
  o More slowing in Type 1 but also seen in Type 2 particularly if poorly controlled and nephropathy which can contribute to the neuropathy
  o Conduction slowing at sites of compression
  o F wave latencies can be prolonged
  o Hard to use EFNS/PNS criteria

• CSF Protein increased in diabetes
  o Japanese study found CSF protein up to 100-125 mg% in diabetics- both with (highest) and without neuropathy
Navigating the Seas of CIDP in Diabetes

You Must Be Particularly Vigilant, Rigorous and Cautious
When to Consider CIDP in Diabetics

1. Meets “Typical CIDP” clinical criteria
   1. Symmetric, proximal and distal weakness
   2. Generalized areflexia- not just ankles
   3. CSF protein > 125 mg%

2. Is “atypical” for length dependent sensory predominant diabetic neuropathy
   1. Aggressive progressive course
   2. Motor involvement not explained by compression such as foot drops or finger extension weakness
When to Consider CIDP in Diabetics: How to Deal with the Nerve Conduction Conundrum

<table>
<thead>
<tr>
<th><strong>DO</strong></th>
<th><strong>DON’T</strong></th>
</tr>
</thead>
</table>
| • ...Put the conduction findings in the clinical context  
• ... Perform studies of the arms  
• ... Perform studies of proximal muscles if distal muscles low amplitude  
• ... Look for temporal dispersion, conduction block, segmental slowing outside of sites of compression | • ...Make diagnosis solely on nerve conduction studies- they have to make sense clinically  
• ...Rely only on changes that are just in the legs  
• ....Rely only on F wave latencies  
• ...Rely on conduction slowing when amplitudes are < 1 MV |
• IVIG probably best option unless you want to deal with increasing blood sugars with corticosteroids
• ICE trial 90% of those who respond to IVIG did so in ~ 2 months- your trial should be no more than 3 months
• Use a dose that gives the best chance of success (eg. ICE trial dosing)
  • 2 gms/kg induction (over 4-5 days)
  • 1 gm/kg every 3 weeks (some advocate 2 weeks) for 3 more treatments
• **USE OBJECTIVE MEASURES OF RESPONSE TO MONITOR**
  • *Do not rely on “I feel more energy”; “My tingling is less”; “My pain is a bit better”*
**Objective Measures That Can Be Used in Clinical Practice: It Takes Only a Few Minutes**

### Validated for CIDP

- **INCAT** (1 minute at most)
- **I- RODS** (3 minutes)
  - 24 question survey
  - Can be done by patient or staff (minimal coaching)
- **Grip strength** (1 minute)
  - Jamar (~ $400)
  - Martin Vigorimeter (Europe)
- **MRC sum score of 16 muscles in arms and legs**

### Not Validated but Still Good for Practice

- **Neurologic Exam**
  - You’re doing it anyway!
  - MRC of involved muscles
  - Reflexes (Do they come back?)
  - Sensory exam (Rydel-Sieffer tuning fork)
- **Gait** (Can Have Staff Do)
  - Timed Up and Go (My favorite)
    - Short
    - Includes getting on and off chair
  - 10 meter walk
  - 6 minute walk
TAKE HOME MESSAGES

- YES- DIABETICS CAN GET CIDP
  - BUT PROBABLY NOT AT INCREASED FREQUENCY
- BE CAUTIOUS IN ATYPICAL CASES
- RECOGNIZE THE CLINICAL AND PHYSIOLOGIC OVERLAPS
- REMEMBER THE PITFALLS IN INTERPRETATION OF CONDUCTION STUDIES
- IF YOU ARE GOING TO TRY A TREATMENT KEEP IT SHORT AND USE OBJECTIVE MEASURES
  - DISCUSS THIS WITH THE PATIENT SO THAT EVERYONE IS ON THE SAME PAGE
Thanks For Listening and Have Smooth Sailing
# 36 Patients Without CIDP

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
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<tbody>
<tr>
<td>EFNS/PNS CIDP clinical criteria</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>11 (30.5)</td>
</tr>
<tr>
<td>Typical</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Atypical</td>
<td>1 (30.5)</td>
</tr>
<tr>
<td>EFNS/PNS CIDP NCS criteria</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>1 (2.7)</td>
</tr>
<tr>
<td>Possible</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Probable</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Definite</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>CSF protein increase (N = 27)</td>
<td>14 (51.8%)</td>
</tr>
<tr>
<td>Mean CSF protein mg/dl (SD, range)</td>
<td>62.6 (29.3, 18–113)</td>
</tr>
<tr>
<td>MRI (N = 27) root/plexus abnormalities,</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Nerve biopsy (N = 6) demyel./remyel</td>
<td>0 (0.0%)</td>
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</tbody>
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