CIDP – life after diagnosis

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Disclosure

Nothing to disclose
“The doctor just told me I have CIDP”

- What is CIDP?
- How common and how serious is CIDP?
- What causes CIDP? Why me?
- What is the prognosis? Is this permanent?
- What does a typical CIDP look like?
- How is the diagnosis made?
- Can I be sure CIDP is the correct diagnosis?
- Am I on the right treatment?
- Will I have to be on treatment for the rest of my life?
- What to do if the treatment does not work?
What is CIDP?
Chronic Inflammatory Demyelinating Polyneuropathy

Polyneuropathy
Many nerves are affected
(Nerves that connect spinal cord and muscles)

Chronic
Occurs over a long period of time (at least > 8 weeks)
(Unlike Guillain-Barre which happens only once)

Inflammatory
Nerve damage due to inflammation
Inflammation is autoimmune (triggered by one’s own immune system)

Demyelinating
Nerve damage affects protein coating (myelin) of the nerve fiber (axon)
How serious is CIDP?

- Serious illness that causes nerve dysfunction
- There is no “cure” but there are very good treatments!
- It causes
  - **Weakness**
  - Sensory symptoms (numbness, tingling...)
  - Pain
  - Balance issues and clumsiness
How common is CIDP?

Rare – prevalence ~ 2-10/100.000

The most common chronic autoimmune neuropathy

Can affect any age (including children)
Peak age 40-60
Men>women
Why me?
What caused my CIDP?

We don’t really know

Not your fault - you did not do anything wrong

Autoimmune

What triggers the immunological attack is not known (unlike Guillain-Barre)

Both cellular and humoral factors are involved

  Cellular – T-cells, cytokines,...

  Humoral – antibodies, complement
Prognosis – the “Big picture”

• Most (9/10) patients respond to one of the treatments
• Many patients are “normal” on treatment

• ~30% of patients achieve remission (no symptoms off treatment) or cure
• ~50% of patients doing well but need treatment
• ~15% not doing well
Is the nerve damage permanent?

Two types of nerve injury in CIDP
1. Demyelination (inflammation)
2. Secondary axon injury (after demyelination)

Deficit caused by damage to the axon (nerve wiring) is permanent

Treatment limits demyelination but there is nothing we can do once the axonal damage done

“Burnout disease” – no more inflammation but deficit from axonal injury persists
What is a “typical” CIDP

• About 6/10 CIDP cases are “typical”

• Weakness is the hallmark of typical CIDP
  
  Symmetric
  
  Proximal weakness (shoulders and hips)
  
  Distal weakness (hands and feet)

• Absent reflexes (ankle and knee jerks)
• Numbness in feet and hands
• Demyelination on EMG
• High protein in in lumbar puncture
• Develops over more than 8 weeks
# What is “Atypical” CIDP

<table>
<thead>
<tr>
<th>Main feature</th>
<th>Another name</th>
<th>Other features</th>
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<tbody>
<tr>
<td>Asymmetric</td>
<td>“MADSAM”</td>
<td>8-15%</td>
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<tr>
<td>Distal</td>
<td>“DADS”</td>
<td>2-10%</td>
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<tr>
<td></td>
<td></td>
<td>With MGUS</td>
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<tr>
<td></td>
<td></td>
<td>With MAG antibodies</td>
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<tr>
<td></td>
<td></td>
<td>Off balance with eyes closed (sensory ataxia)</td>
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<tr>
<td>Motor predominant</td>
<td>No sensory symptoms</td>
<td></td>
</tr>
<tr>
<td>Sensory predominant</td>
<td>No weakness</td>
<td></td>
</tr>
<tr>
<td>“Acute” CIDP</td>
<td>A-CIDP</td>
<td>4-10%</td>
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<td></td>
<td></td>
<td>Starts as Guillain-Barre</td>
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<tr>
<td>CANOMAD</td>
<td></td>
<td>Double vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trouble swallowing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sensory ataxia</td>
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</table>
Red flags and mimics: What is NOT CIDP?

- Bladder or bowel issues
- Very severe pain
- Double vision and swallowing trouble
- Swelling
- Rash, fever, weight loss....

CIDP “Mimics”
- Diabetic neuropathy – can have some demyelinating features
- Inherited neuropathy – look at the feet
- Miscellaneous
  - Muscle diseases
  - Neuromuscular junction disease (Myasthenia)
How is the diagnosis made?

Important: there is no “gold standard” test
We rely on the combination of the following:

**BASICS**
- History (including your family history)
- Exam (strength, reflexes, sensation)
- Basic laboratories (tests for diabetes, MGUS, kidney function,.....)

**NERVE CONDUCTION STUDY/EMG**
- Combination of demyelination in several nerves not explained by another process

**LUMBAR PUNCTURE or nerve biopsy**
- LP – high protein (antibodies in spinal fluid) but no cells
- Biopsy – very rarely done for CIDP
NCS/EMG

Very important for the diagnosis
Documents demyelination
Every CIDP patient should have at least one good-quality EMG
EMG is not an X-ray
Who interprets it in real-time matters
There are “good” EMGs and “bad” EMGs

There are diagnostic criteria
16 sets of criteria
Not used enough
EFNS/PNS criteria
Sensitivity 81% - 19%: Pos CIDP but Neg criteria
Specificity 96% - 4%: Pos criteria but Neg CIDP
NCS/EMG – how are they done?

<table>
<thead>
<tr>
<th>Nerve / Sites</th>
<th>Rec. Site</th>
<th>Lat. ms</th>
<th>Amp mV</th>
<th>Rel Amp %</th>
<th>Dist cm</th>
<th>Velocity m/s</th>
<th>Temp °C</th>
<th>Segments</th>
<th>Dur. ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>L MEDIAN - APB</td>
<td>Wrist</td>
<td>4.45</td>
<td>9.6</td>
<td>100</td>
<td>6</td>
<td>29.6</td>
<td></td>
<td>Wrist - APB</td>
<td>6.10</td>
</tr>
<tr>
<td></td>
<td>Elbow</td>
<td>9.55</td>
<td>9.3</td>
<td>96.7</td>
<td>23</td>
<td>45.1</td>
<td>29.8</td>
<td>Elbow - Wrist</td>
<td>6.05</td>
</tr>
</tbody>
</table>
NCS/EMG – what are we looking for?

Conduction “Block”
Temporal dispersion
Slower conduction velocity
Is lumbar puncture necessary?

I do it in majority of patients (8/10)

I do not do LP if

Typical story + exam
Typical EMG
Responding to treatment
Some other reason not to do LP (blood thinners, history of bad reaction to LP, patient really opposed to it...)

Beth Israel Lahey Health
Lahey Hospital & Medical Center
How do I know that the diagnosis is correct?  
The issue of misdiagnosis

Excellent question!!

CIDP misdiagnosis = patient diagnosed and treated for CIDP, but does not have CIDP

There is a high rate of CIDP misdiagnosis

Why is misdiagnosis a big problem?  
- Treatment can have side effects  
- Treatment is expensive  
- You are being treated for the disease that you have!
How do I know that the diagnosis is correct?
The issue of misdiagnosis

Important study published in 2015 (Allen & Lewis, 2015)

Retrospective review of 59 patients referred for second opinion of CIDP

47% (27/58) DID NOT have CIDP
53% (31/58): CIDP confirmed

Diagnosis more likely to be correct if seen by neuromuscular specialist
More on the issue of misdiagnosis

Alternative diagnoses

More common
- Diabetic neuropathy, ALS, Fibromyalgia, Small-fiber neuropathy, Hereditary neuropathy

Others
- Multiple sclerosis, alcohol, multifocal motor neuropathy, myopathy, stiff person syndrome

Reasons for misdiagnosis

EMG: Overinterpretation of conduction slowing in diabetics and at certain sites
LP: Emphasizing mild increase in CSF protein

Message
The diagnosis SHOULD NOT rest on EMG or LP alone!

Allen JA, 2015
Diagnostic data in CIDP and Non-CIDP patients
Response to treatment

<table>
<thead>
<tr>
<th></th>
<th>Clinical</th>
<th>Improved with treatment</th>
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<tbody>
<tr>
<td>CIDP</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>Non-CIDP</td>
<td>44%</td>
<td>86%</td>
</tr>
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</table>

CIDP Treatment makes non-CIDP patients feel better (we know this about corticosteroids and IvIg) but doesn’t improve the disease

Allen JA, 2015
Treatment of CIDP
Proven and unproven therapies

Proven first line CIDP Treatments
1. IVIG (Intravenous immunoglobulin)
2. Corticosteroids
3. Plasma exchange

EVERYTHING ELSE is UNPROVEN
Metotrexate, Cyclosporine, Azathioprine (Imuran), Mycophenolate (Cellcept), Cyclophosphamide (Cytoxan),...
These SHOULD NOT be your first or second treatment
They work in some patients
CIDP treatments
General principles and issues

IVIG, corticosteroids and plasma exchange roughly equivalent
Proven to induce short-term improvement
CIDP is a chronic disease – less clear which drugs more likely to maintain improvement
50-80% of patients respond to the first treatment
Some respond to one therapy but the others
10-15% of patients do not respond to anything
10-15% of patients may need no further treatment after initial response
CIDP Treatment

IVIg

First line for most (well tolerated)
IVIg may be the only treatment needed (10-15% need 1-2 tx for remission)
3 treatments are needed to see if IVIg works
Majority of patients with CIDP will respond (~75% per Kuitwaard 2015)

FDA-approved regimen (per ICE trial)
- Loading dose: 2 gm/kg over 2-5 days
- Maintenance: 1gm/kg every 3 weeks (over 1-2 days) for 6 months

It is common that IVIg is not use the right way
- Both undertreatment (too little) and overtreatment (too long) common
What is IVIg and how does IVIg work?

Blood plasma pooled from thousands of blood donors
Source of “good antibodies” that counteract “bad antibodies”

IVIg *modulates* your immune system, it does not *suppress* it

Some of the possible mechanisms of immune modulation by IVIg in CIDP
- Modulates inflammatory and anti-inflammatory cytokines
- Modulates Fc receptors on macrophages
- Inhibits complement
- “neutralizes” bad antibodies (antibodies against antibodies)
IVIg – Side effects

Serious side effects very rare
Mild side effects common but manageable

Of all “heavy duty” immunological drugs, IVIg is as gentle as it gets

Common side effects
  Malaise, fatigue
  Headache (can be prevented by premedications and slower rate)

Less common
  Rash – allergic rash and other types of rashes (dyshidrotic eczema, psoriasis)
  Aseptic meningitis – not the deadly type of meningitis but really bad headache

Rare but serious
  Stroke, heart attack, blood clot, kidney failure
IVIg – Side effects
What if I’m having problems tolerating it?

Am I being premedicated before the infusion (steroids, fluids, benadryl)

Can my infusion rate be slower?

Is my infusion slow at first and then increased slowly?

Was my brand recently changed?

Could I get more fluids before and after?
Do I have to be on IVIg forever?

It is common that IVIg is used for too long

IVIg SHOULD NOT be an open-ended treatment forever
Discussion about IVIg taper → should be discussed during the first IVIg talk with your doctor

ICE trial (the one that led to FDA approval)

IVIg stopped after 6 months

54% of patients improved at 6 months

At 12 months, ~50% still maintained their improvement
How to stop or taper IVIg?

When to stop?

- When remission reached (no symptoms)
- If no response after 3 treatments
- After ~ 6 months

Relapse is not always a bad thing but a part of treatment process

We want to treat only those who are IVIg dependent

How to taper?

- No single right way
- Approach #1: Decrease the dose (20%), same interval
- Approach #2: Stretch the interval, same dose
- Relapse: Retreat with 2gm/kg and continue with the dose/interval before relapse
- Try again after several months of stability
Subcutaneous immunoglobulin
SCIG

Administered through needles in the skin instead of intravenously
Has been used in other areas of medicine for decades
Recent FDA approval for CIDP (maintenance treatment)

Pros
No IV needed
Can be done by patients at home (autonomy)
?Fewer side effects (headache)
More patients prefer it over IVIg

Cons
Infusions on 3-4 days per week VERSUS ½ day on IVIG once every 3-4 weeks?
Figuring out the dose (IV→SQ) can be a process
Can be tough if you have hand weakness
Subcutaneous immunoglobulin
SClg

Maintenance treatment
FDA approved in 2018 (Hizentra) to maintain improvement after IVlg (or another first line therapy)

Can SClg be used as the first line treatment?
Maybe
Single small but good Danish study
0.4 gm/kg weekly x 5 weeks (2-3 infusions per week)
As good as IVIG but IVIG works faster (max improvement 2 versus 5 weeks)
Corticosteroids

Traditional
   Prednisone pills 1 mg/kg (~ 60-100 mg a day)

“Pulse” treatment (large dose given occasionally)
   Dexamethasone pills 40 mg x 4 days each month
   Intravenous Solumedrol (500-1000 mg weekly or monthly)

Improvement can be rapid (~ weeks) but usually slow (~ 2 months)

IVIg versus corticosteroids
   IVIg may work faster
   IVIg is better tolerated
   Corticosteroids are cheaper
   Corticosteroids may be more likely to lead to remission (25% off treatment 5 years after 1-2 dexamethasone treatments)
Side effects – the main problem with corticosteroids

Weight gain
Insomnia
Osteoporosis
Diabetes
Hypertension
Depression
Irritability
Stomach ulcers
Cataracts
Increased risk for infections

Daily prednisone for a long time has most side effects

“Pulse” treatments probably fewer long term side effects
“Pulse” treatments may have short term side effects (insomnia, restlessness,...)
Corticosteroids – how to taper
Management of side effects

Taper should be attempted continuously
Taper has to be gradual (over months)
Sudden stop can be life threatening
Taper can be done on alternate day (odd day, even day)
Question long-term prednisone > 20 mg daily

Osteoporosis
• Dexe scan before treatment and yearly
• Calcium and vitamin D daily
• If Dexe abnormal, your PCP should consider Fosamax

Preventative antibiotics if on prednisone > 20 mg a day (Bactrim)

Keep moving – prednisone exacerbates weakness from deconditioning
Plasma Exchange

Clearly works and works quickly

Not a practical solution for long-term management

Issues
  Need for central line
  Huge fluid shifts
  Limited resource

Still the choice for a rapidly deteriorating patient (rapid onset of action)

200-250 mL/kg over 5-6 treatments over 2 weeks
Other agents in CIDP

Many immunosuppressants
None is “proven” but may work in an individual patient
These are strong drugs with serious side effects

When to consider them?

*If no response to first-line treatments*
*Add-on if unable to taper steroids or IVIg*

Cyclosporine
Metotrexate
Axathioprine (Imuran)
Mycophenolate (Cellcept)
Cyclophosphamide (Cytoxan)
Rituximab (Rituxan)
How does my doctor monitor my progress?

"Feeling better" is not good enough and should not guide treatment!

Meanigful improvement of CIDP justifies potentially harmful and expensive drugs

Meanigful improvement in daily activities (stairs, shower, driving,....)

Exam scales (MRC sumscore measuring your strength)

Quantitative tests
   TUG – timed up and go

Measurement tools
   Jamar grip meter

Patient-reported scales - IRODS
How does my doctor monitor my progress?

### IRODS

<table>
<thead>
<tr>
<th>Task</th>
<th>Not possible to perform</th>
<th>Possible, but with some difficulty</th>
<th>Possible, without any difficulty</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. read a newspaper/book?</td>
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<tr>
<td>2. eat?</td>
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<tr>
<td>3. brush your teeth?</td>
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<td>4. wash upper body?</td>
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<tr>
<td>5. sit on a toilet?</td>
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<tr>
<td>6. make a sandwich?</td>
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<tr>
<td>7. dress upper body?</td>
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<td></td>
<td></td>
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<tr>
<td>8. wash lower body?</td>
<td></td>
<td></td>
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<tr>
<td>9. move a chair?</td>
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<td></td>
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<tr>
<td>10. turn a key in a lock?</td>
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<tr>
<td>11. go to the general practitioner?</td>
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<tr>
<td>12. take a shower?</td>
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<tr>
<td>13. do the dishes?</td>
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<td></td>
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<tr>
<td>14. do the shopping?</td>
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<td></td>
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<tr>
<td>15. catch an object (e.g., ball)?</td>
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<tr>
<td>16. bend and pick up an object?</td>
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<tr>
<td>17. walk one flight of stairs?</td>
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<tr>
<td>18. travel by public transportation?</td>
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<tr>
<td>19. walk and avoid obstacles?</td>
<td></td>
<td></td>
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<tr>
<td>20. walk outdoor &lt; 1 km?</td>
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<tr>
<td>21. carry and put down a heavy object?</td>
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<tr>
<td>22. dance?</td>
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<tr>
<td>23. stand for hours?</td>
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<tr>
<td>24. run?</td>
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What if my treatment doesn’t work

Improved but not enough

- Sometimes waiting is the good option
- Am I getting too little?
- Try another first-line treatment
  
  *Most patients respond to IVIG*
  
  > *half of non-responders respond to PE or steroids*
  
  *Non-responders to 2 modalities may still respond to the 3rd*

No response

- Review diagnosis
- Try different first-line treatment

Adverse effect

- Change something (premedication, different infusion rate...)
- Try different first-line treatment
Ask for another opinion if

On CIDP treatment but your clinical features are “atypical

If CIDP diagnosis based mainly on EMG

If diabetic

If not improved after 3 months of IVIg and/or steroids
Thank you!