Chronic Inflammatory Demyelinating Polyneuropathy

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Chronic Immune Demyelinating Polyneuropathy

- Acquired autoimmune neuropathy
- Affects all ages (increasing prevalence/incidence with age)[1]
- Male predominance[1]
- Reported prevalence 0.67-10.3 per 100,000[1]
- Risk factors unknown

1. Broers MC et al. Incidence and Prevalence of CIDP. Neuroepidemiology 2019

Clinical Features

Symmetric motor and sensory involvement

- Motor: proximal and distal weakness
- Sensation: Vibration/position > pain/temperature; distal>proximal
- Diminished or absent reflexes
- Less frequent than GBS: facial/cranial nerve, respiratory, or autonomic involvement[1,2]
- Low back pain may be present

1. Ruts L, Drenthen J, Jacobs BC, van Doorn PA. Distinguishing acute-onset CIDP from fluctuating GBS. Neurology 2010
2. Dionne A et al. Clinical and electrophysiological parameters distinguishing acute-onset CIDP from AIDP. Muscle Nerve 2010

Clinical Features

Time course

- Slowly progressive or relapsing-remitting (younger age)
- Symptom progression >8 weeks
- Up to 16% evolve acutely[1]

1. McCombe PA et al. CIDP: a clinical and electrophysiological study of 92 cases. Brain 1987

Atypical Variants

- **Asymmetric**
- **Distal predominant**
- Focal
- Motor predominant
- Sensory predominant
- **CIDP phenotype with IgG4 antibodies against nodal/paranodal proteins**

Bunschoten C, et al. Progress in diagnosis and treatment of CIDP. Lancet Neurol 2019.

Asymmetric Variant

- Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)
- Also known as Lewis-Sumner syndrome
- Similar to mononeuropathy multiplex - individual nerve distributions affected
- Chronic
- Distal > proximal
- Upper > lower limbs

Bunschoten C et al. Progress in diagnosis and treatment of CIDP. Lancet Neurol 2019
Lewis RA, Sumner AJ, Brown MJ, Asbury AK. Multifocal demyelinating neuropathy with persistent conduction block. Neurology 1982
Rajabally YA, Chavada G. Lewis-sumner syndrome of pure upper-limb onset. Muscle Nerve 2009

Distal Predominant Variant

- Distal acquired demyelinating symmetric neuropathy (DADS)
- Slowly progressive, symmetric, sensory-predominant symptoms[1]
- Male-predominant[1]
- Frequently associated with IgM paraprotein

DADS with IgM paraprotein - considered distinct from CIDP

- About 50% also have anti-MAG antibodies[1]
- No improvement with standard immunotherapy treatment[2]

1. Katz JS et al. Distal acquired demyelinating symmetric neuropathy. Neurology 2000
2. Lunn MP, Mobile-Orazio E. Immunotherapy for IgM anti-MAG paraprotein-associated peripheral neuropathies. Cochrane Database Syst Rev 2016.

Nodal/Paranodal IgG4 Antibodies

- Contactin-associated protein 1 (CASPR1)[1]
- Contactin-1 (CNTN1)[2]
  - Severe motor phenotype[2]
  - Less likely to improve with IV immune globulin therapy (IVIg)
  - May respond to B cell depletion therapy (rituximab)
- Neurofascin (NF155, NF140, NF186)
  - NF155: younger, sensory ataxia, tremor, poor response to IVIg [3]
  - NF140, NF186: sensory ataxia[4]

1. Doppler et al. Auto-antibodies to contactin-associated protein 1 in two patients with painful inflammatory neuropathy. Brain 2016.
2. Miura et al. Contactin 1 IgG4 associates to CIDP with sensory ataxia. Brain 2015.
3. Devaux et al. Neurofascin-155 IgG4 in CIDP. Neurology 2016
4. Delmont et al. Autoantibodies to nodal isoforms of neurofascin in CIDP. Brain 2017

.

Diagnostics

History and exam:

- Progressive sensory and motor deficits > 8 weeks
- Proximal and distal weakness
- Absent or reduced reflexes

- Evaluate for genetic cause

Studies:

- Electrodiagnostic testing (NCS/EMG)
- Labs

Supportive:

- Cerebrospinal fluid (CSF) analysis
- Imaging (MRI with gadolinium)
- Nerve biopsy

Labs

- Serum protein electrophoresis (SPEP) PLUS serum immunofixation
- Hemoglobin A1c, fasting serum glucose, or glucose tolerance test
- Vitamin B12 level
- CBC, complete metabolic panel
- Thyroid function studies

- HIV antibody, hepatitis profiles, Lyme
- ANCA, SSAB, RF, ACE, ESR/CRP

1. Barohn et al. CIDP: clinical characteristics, course, and recommendations for diagnostic criteria. Arch Neurol 1989.

Labs

- Ensure testing of SPEP and serum immunofixation
- MAG antibody
- IgM (+/- MAG antibody) – refractory to therapy
- IgA, IgG lambda – POEMS syndrome
- If negative, always retest if refractory to traditional CIDP therapy

Additional Diagnostics

CSF analysis:

- Elevated CSF protein in majority[1]
- Normal white cell count

MRI with gadolinium contrast

- Spinal roots, cauda equina, brachial and lumbosacral plexus
- May see enlarged/enhancing nerves[2]

Nerve biopsy

- Evaluate for alternative diagnosis
- Limited diagnostic value for CIDP

1. Barohn et al. CIDP: clinical characteristics, course, and recommendations for diagnostic criteria. Arch Neurol 1989.
2. Ishikawa et al. MR neurography for the evaluation of CIDP. Muscle nerve 2017.

Diagnostic Criteria

- No gold standard for diagnosis
- Over 15 sets of criteria
- European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS) 2010 criteria

EFNS/PNS 2010 Criteria

- Clinical criteria: Typical or atypical
- Electrodiagnostic criteria: Definite, probable, possible
- Supportive criteria
- Overall: Definite, Probable, Possible CIDP

Van den Bergh PYK et al. EFNS/PNS guideline on management of CIDP-first revision. Eur J Neurol 2010

EFNS/PNS 2010 Criteria

Table 4. Clinical diagnostic criteria.

(1) Inclusion criteria
  (a) Typical CIDP
    Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and
    Absent or reduced tendon reflexes in all extremities
  (b) Atypical CIDP (still considered CIDP but with different features) One of the following, but otherwise as in (a) (tendon reflexes may be normal in unaffected limbs):
    Predominantly distal (distal acquired demyelinating symmetric, DADS) or
    Asymmetric [multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis-Sumner syndrome] or
    Focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb)
    Pure motor or
    Pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron)
(2) Exclusion criteria
  Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy
  Hereditary demyelinating neuropathy
  Prominent sphincter disturbance
  Diagnosis of multifocal motor neuropathy
  IgM monoclonal gammopathy with high titre antibodies to myelin-associated glycoprotein
  Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy. PNS lymphoma and amyloidosis may occasionally have demyelinating features

EFNS/PNS 2010 Criteria

Table 1. Electrodiagnostic criteria.

(1) Definite: at least one of the following
  (a) Motor distal latency prolongation ≥50% above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or
  (b) Reduction of motor conduction velocity ≥30% below LLN in two nerves, or
  (c) Prolongation of F-wave latency ≥30% above ULN in two nerves (≥50% if amplitude of distal negative peak CMAP <80% of LLN values), or
  (d) Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes ≥20% of LLN + ≥1 other demyelinating parameter[a] in ≥1 other nerve, or
  (e) Partial motor conduction block: ≥50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter[a] in ≥1 other nerve, or
  (f) Abnormal temporal dispersion (>30% duration increase between the proximal and distal negative peak CMAP) in ≥2 nerves, or
  (g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥1 nerve (median ≥ 6.6 ms, ulnar ≥ 6.7 ms, peroneal ≥ 7.6 ms, tibial ≥ 8.8 ms)[b] + ≥1 other demyelinating parameter[a] in ≥1 other nerve
(2) Probable
  ≥30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter[a] in ≥1 other nerve
(3) Possible
  As in (1) but in only one nerve
  To apply these criteria, the median, ulnar (stimulated below the elbow), peroneal (stimulated below the fibular head), and tibial nerves on one side are tested. If criteria are not fulfilled, the same nerves are tested at the other side, and/or the ulnar and median nerves are stimulated bilaterally at the axilla and at Erb's point. Motor conduction block is not considered in the ulnar nerve across the elbow and at least 50% amplitude reduction between Erb's point and the wrist is required for probable conduction block. Temperatures should be maintained to at least 33°C at the palm and 30°C at the external malleolus (good practice points).
  CMAP, compound muscle action potential; ULN, upper limit of normal values; LLN, lower limit of normal values.

[a]Any nerve meeting any of the criteria (a–g).
[b]Isose S. *et al. (Isose et al., 2009).*

EFNS/PNS 2010 Criteria

Table 5. Supportive criteria.

1. Elevated CSF protein with leukocyte count $<10/mm^3$ (level A recommendation)
2. MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses (level C recommendation)
3. Abnormal sensory electrophysiology in at least one nerve (Good Practice Points):
   a. Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial sensory nerve action potential (SNAP) amplitudes; or
   b. Conduction velocity <80% of lower limit of normal (<70% if SNAP amplitude <80% of lower limit of normal); or
   c. Delayed somatosensory evoked potentials without central nervous system disease
4. Objective clinical improvement following immunomodulatory treatment (level A recommendation)
5. Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fibre analysis (Good Practice Points)

EFNS/PNS 2010 Criteria

Table 6. Diagnostic categories.

Definite CIDP
Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 1; or
Probable CIDP + at least one supportive criterion; or
Possible CIDP + at least two supportive criteria
Probable CIDP
Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 2; or
Possible CIDP + at least one supportive criterion
Possible CIDP
Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 3
CIDP (definite, probable, possible) associated with concomitant diseases.

Diagnostic Pitfalls

Over-diagnosis, misdiagnosis are common[1]

- Failure to adhere to clinical criteria
- Misinterpreted electrodiagnostic studies[2]
- Reliance on patient-reported benefit of treatment
- Overemphasis on cytoalbuminologic dissociation

Erroneous diagnosis leads to unnecessary treatment[3]

1. Allen JA, Lewis RA. CIDP diagnostic pitfalls and perception of treatment benefit. Neurology 2015
2. Allen JA et la. Electrodiagnostic errors contribute to CIDP misdiagnosis. Muscle Nerve 2018
3. Cornblath et al. Observations on CIDP. J Neurol Sci 2013.

Therapies

- Steroids
- Intravenous immunoglobulin (IVIg), subcutaneous immunoglobulin (SCIg)
- Plasma exchange
- Additional agents

- First line – Steroids or IVIg[1]

1. Van den Bergh PYK et al. EFNS/PNS guideline on management of CIDP-first revision. Eur J Neurol 2010

Steroids

- Oral prednisone or prednisolone
  - Initial high dose
  - Maintenance: slowly tapering over weeks, every other day
- Pulsed oral dexamethasone
- Pulsed IV methylprednisolone

- Several regimens are equally effective[1,2]
- Potentially fewer side effects with pulsed regimen[1,3]

1. Van Schaik IN et al. PREDICT study. Lancet Neurol 2010
2. van Lieverloo et al. Corticosteroids in CIDP. J Neurol 2018
3. Lopate G et al. Treatment of CIDP with high dose intermittent intravenous methylprednisolone. Arch Neurol 2005

IVIg

- Initiation 2g/kg (over 2-5 days)
- Maintenance dose:
  - 0.4g/kg to 1.2g/kg every 2-6 weeks[1]
  - 1g/kg every 3 weeks (ICE trial)[2]
- Similar efficacy to plasma exchange, steroids[3]
- 76% of treatment-naïve are responders[4]
- Less frequently discontinued than IV methylprednisolone[5]

1. Van den Bergh PYK et al. ENFS/PNS guideline on management of CIDP- first revision. Eur J Neurol 2010
2. Hughes et al. IVIg for the treatment of CIDP (ICE study). Lancet Neurol 2008
3. Eftimov et al. IVIg for CIDP. Cochrane Database Syst Rev. 2013
4. Kuitwaard et al. J Neurol Neurosurg Psychiatry 2015
5. Nobile-Orazio et al. IVIg versus IV methylprednisolone for CIDP. Lancet Neurol 2012

Subcutaneous Immunoglobulin

PATH trial[1]

- Efficacious for maintenance (in patients previously dependent on IVIg)
- 0.2g/kg or 0.4g/kg weekly doses
- Highly effective in preventing relapse compared to placebo
- No severe headache, thrombosis, or renal side-effects
- Infusion site reactions minor
- No issues with IV access

1. van Schaik IN et al. Subcutaneous immunoglobulin for maintenance treatment in CIDP (PATH). Lancet Neurol 2018.

Subcutaneous Immunoglobulin

- Cheaper (self-administered)
- Consider in patients with:
  - Severe headache with IVIg infusions
  - Difficult IV access
- Is SCIg as effective as IVIg as maintenance therapy?

Plasma Exchange

- 5-10 sessions within 2-4 weeks on alternate days[1,2]
- Less frequently used
  - Venous access
  - Relatively invasive
  - Limited availability of facilities
- Consider if IVIg and corticosteroids are ineffective[3]

1. Mehndiratta et al. Plasma exchange for CIDP. Cochrane Database Syst Rev 2015
2. Oaklander et al. Treatments fo CIDP: an overview of systemic reviews. Cochrane Database Syst Rev 2017
3. Van den Bergh PYK et al. EFNS/PNS guideline on management of CIDP-first revision. Eur J Neurol 2010

Additional Agents

Consider when inadequate benefit from corticosteroids, IVIg, or plasma exchange[1]

No benefit in any randomized controlled trial[2]

- Azathioprine
- Mycophenolate mofetil
- Methotrexate
- Cyclosporine
- Tacrolimus
- Rituximab, Cyclophosphamide

1. Van den Bergh PYK et al. EFNS/PNS guideline on management of CIDP-first revision. Eur J Neurol 2010
2. Mahdi-Rogers et al. Cochrane Database Syst Rev 2017

Therapy

- Approximately 15% do not respond to any treatment[1]
- May improve with a second proven effective treatment if first-line ineffective
- **<u>Reconsider diagnosis of CIDP</u> if no improvement with IVIg and steroids**
  - Re-send SPEP, serum immunofixation, MAG antibodies
  - Atypical distal predominant (DADS) variant, IgM +/- anti-MAG antibody: no improvement
  - POEMS: IgG or IgA lambda, elevated VEGF level, abnormal skeletal survey (osteosclerotic myeloma)

1. Van den Bergh PYK et al. EFNS/PNS guideline on management of CIDP-first revision. Eur J Neurol 2010

Measuring Response

- Avoid relying on patient-reported subjective improvement[1] in numbness, pain, or fatigue
- Rely on objective measures
  - Manual Muscle Testing
  - Grip strength
  - Functional tests
  - Quantitative sensory measures (vibration)
  - Triple Timed-up-and-go (3TUG)
  - Use of assistive devices

1. Allen JA, Lewis RA. CIDP diagnostic pitfalls and perception of treatment benefit. Neurology 2015

Maintenance Therapy

- Corticosteroids: 12+ weeks at starting dose then slowly taper
- IVIg: reduce dose/frequency once stable
  - 15-30% require only a single course[1]
  - ICE trial and other placebo arms: 30-40% discontinue IVIg without relapse
  - After 6 months (or plateau of clinical improvement), trial dose reduction
  - If unsuccessful, retry periodically
- Do not treat inactive disease (follow objective measures)

1. Van den Bergh PYK et al. EFNS/PNS guideline on management of CIDP-first revision. Eur J Neurol 2010

Summary

- Acquired immune-mediated neuropathy
- Subacute (>8 weeks) proximal and distal motor weakness, sensory abnormalities, and absent/diminished reflexes
- Diagnostic studies: EMG, labs
- LP, MRI, nerve biopsy if needed
- Avoid over-diagnosis
- First line therapy: IVIg or corticosteroids – reconsider diagnosis if no improvement
- Maintenance therapy: continually reassess need, reduce to lowest effective dose
- Avoid over-treatment

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