WEAKNESS, NUMBNESS AND PAIN IS THIS NEUROPATHY?

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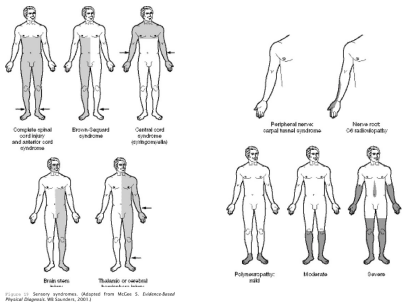
CONTENT

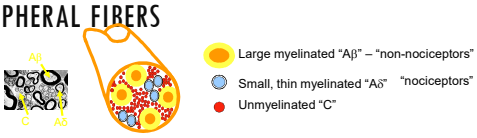
Clinical approach:
- large vs small fiber neuropathy
- Motor vs sensory polyneuropathy
- Axonal vs demyelinating neuropathy
- Mimics: neuronopathy, motor neuron lesion, etc

Types and common causes of
- Axonal type: systemic, toxic/metabolic diseases
- Demyelinating type: CIDP, CMT disease

Investigations and treatment guidelines in common diseases



PERIPHERAL FIBERS



Fiber type	Properties	Velocity (m/s)	Function	Perception
Aβ (large)	Myelinated	30–70	Touch Pressure Vibration	Sharp Well localized
Aδ (small)	Myelinated	5–30	**Pain** (pinprick) Temperature (cold threshold)	Sharp Well localized
C (small)	Unmyelinated	≤1	**Pain** (Temperature/ pressure/ chemical)	Dull Poorly localized Persistent

1. Basbaum et al, In: Kandel et al. eds. *Principles of Neural Science* 4th ed. 2000:473-77.
2. Basbaum et al, In: Stoelting. *Pharmacology and Physiology* 3rd ed. 1999:482-83.

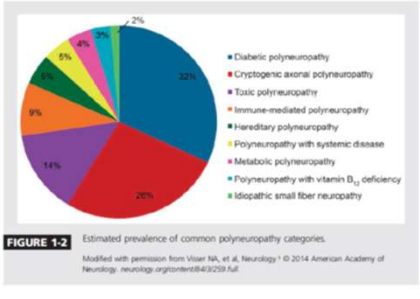


FIGURE 1-2 Estimated prevalence of common polyneuropathy categories.

Modified with permission from Visser NA, et al, Neurology® © 2014 American Academy of Neurology. neurology.org/content/84/3/259.full

MORE INTENSIVE EVALUATION: RED FLAGS

Acute to subacute onset
Rapid progression
Motor predominance
Non-length dependence
Associated dysautonomia
Associated systemic disease

TABLE 1-4 Motor Neuropathies/Neuronopathies

Pattern	Notable Examples
Length-dependent pure motor	Hereditary motor neuropathy, hereditary spastic paraparesis (some genotypes)
Length-dependent motor predominant	Charcot-Marie-Tooth disease, toxins (arsenic, lead)
Monomelic	Benign focal amyotrophy/monomelic amyotrophy
Monomelic progressing to generalized	Amyotrophic lateral sclerosis/progressive muscular atrophy, infectious (polio/postpolio/West Nile virus/enterovirus D68), paraneoplastic (rare)
Proximal symmetric/ generalized	Spinal muscular atrophy, acute motor axonal neuropathy (Guillain-Barré variant), hexosaminidase deficiency
Multifocal	Multifocal motor neuropathy (MMN)

Continuum (Minneap Minn) 2017;23(5):1241–1262

TABLE 10-4 Causes of Small and Large Fiber Sensory Neuropathies

Etiology	Evaluation
Diabetes mellitus	Glycosylated hemoglobin, fasting glucose, 2-hour glucose tolerance
Sporadic amyloidosis	Serum and urine protein electrophoresis, immunofixation, light chains, fat aspirate, rectal mucosa biopsy, or nerve biopsy with Congo red staining
Sjögren syndrome	Sicca symptoms, anti-Ro (SSA)/anti-La (SSB) antibodies, rose bengal test, Schirmer test, lip/salivary gland biopsy
Celiac disease	Antigliadin antibodies (serum IgA endomysial and tissue transglutaminase antibody), IgG-deamidated gliadin peptides, small bowel biopsy, testing for HLA DQ2/DQ8
Sarcoidosis	Chest x-ray, serum angiotensin-converting enzyme, lymph node or other tissue biopsy for necrotizing granulomas
Leprosy	Serum antibodies to PGL-1, skin biopsy or nerve biopsy for acid-fast bacilli
Systemic lupus erythematosus	ANA, antiphospholipid antibodies, complement levels, ESR, CRP, anti-dsDNA and anti-Smith antibodies
Sensory chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Diagnosis is supported by nerve conduction studies and CSF analysis
Human immunodeficiency virus (HIV)	Fourth-generation antigen/antibody immunoassay, HIV viral load testing
Hepatitis C virus	Anti- hepatitis C virus antibody, hepatitis C virus RNA
Cryoglobulinemia (typically associated with hepatitis C virus)	Cryoglobulin levels, hepatitis C virus antibody and PCR
Lyme disease	Tick exposure, serum ELISA with Western blot confirmation
Vitamin deficiencies	Vitamin B_{12} and methylmalonic acid levels; folic acid, vitamin E, vitamin B_6 and thiamine levels

Tangier disease	ATP binding cassette (ABC) transporter mutation
Toxins	Chemotherapy (taxols, platinum drugs, bortezomib), metronidazole, phenytoin, ethambutol, isoniazid, thallium, mercury, lead
Alcohol	History of drinking alcohol
Hypothyroidism	TSH, free T4 levels
Hereditary neuropathies	Genetic testing for hereditary sensory and autonomic neuropathies, mitochondrial mutation testing
Familial amyloid	Genetic testing for transthyretin (*TTR*), apolipoprotein A1 (*APOA1*), and gelsolin (*GSN*) mutations
Paraneoplastic	Voltage-gated potassium channel antibodies (CASPR2 specifically), anti-Hu antibodies, anti-CV2/CRMP-5 antibodies
Other antibody-mediated	Sulfatide antibodies, GD1b antibodies, anti-galactocerebroside antibodies
Idiopathic	Diagnosis of exclusion

ANA = antinuclear antibody; ATP = adenosine triphosphate; CASPR2 = contactin-associated proteinlike 2; CRMP-5 = collapsin response mediator protein-5; CRP = C-reactive protein; CSF = cerebrospinal fluid; dsDNA = double-stranded deoxyribonucleic acid; ELISA = enzyme-linked immunosorbent assay; ESR = erythrocyte sedimentation rate; HLA = human leukocyte antigen; IgA = immunoglobulin A; IgG = immunoglobulin G; PCR = polymerase chain reaction; PGL-1 = phenolic glycolipid-1; RNA = ribonucleic acid; SSA = Sjögren syndrome A; SSB = Sjögren syndrome B; T4 = thyroxine; TSH = thyroid-stimulating hormone.

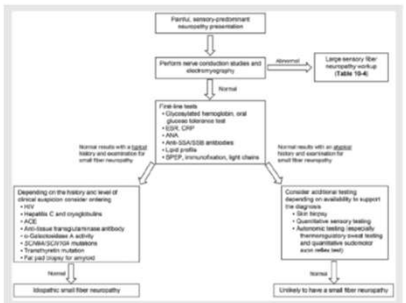


FIGURE 10-1 A diagnostic algorithm for small fiber neuropathies.

ACE = angiotensin-converting enzyme; ANA = antinuclear antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HIV = human immunodeficiency virus; SPEP = serum protein electrophoresis; SSA = Sjögren syndrome A; SSB = Sjögren syndrome B.

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TABLE 1-3 Sensory Neuronopathies*

Categories	Notable Examples	% of Sensory Neuropathy Patients	% of Patients With the Disease Who Have Sensory Neuropathy
Idiopathic	NA	50	NA
Inflammatory/ immune mediated	Sjögren syndrome	5	39
	Paraneoplastic sensory neuronopathy (anti-Hu positive)	Unknown	74
	Autoimmune hepatitis	Unknown	Unknown
Toxic	Pyridoxine toxicity	Unknown	Unknown
	Platin chemotherapy	Unknown	Unknown
Infectious	Herpes zoster	Unknown	Unknown
	Epstein-Barr virus	Unknown	Unknown
	Human T-cell lymphotropic virus type 1 (HTLV-1)	Unknown	Unknown
	Human immunodeficiency virus (HIV)	Unknown	Unknown
Hereditary/ degenerative	Mitochondrial: polymerase γ (POLG), sensory ataxic neuropathy, dysarthria, and ophthalmoplegia (SANDO)	Unknown	Unknown
	Cerebellar ataxia, neuronopathy, vestibular ataxia syndrome (CANVAS)	Unknown	Unknown
	Spinocerebellar degeneration	Unknown	Unknown
	Facial-onset sensory and motor neuropathy (FOSMN)	Unknown	Unknown

NA = not applicable.

* Data from Gwathmey KG, Muscle Nerve.[18] onlinelibrary.wiley.com/doi/10.1002/mus.24943/full.

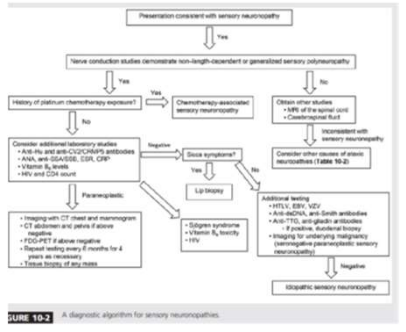


FIGURE 10-2 A diagnostic algorithm for sensory neuronopathies.

Continuum (Minneap Minn) 2017;23(5):1311–1336

TABLE 1-10 Serologic Markers With Clinical Utility in Peripheral Neuropathy Evaluation

Phenotype	Autoantibodies	Sensitivity
Acute motor axonal neuropathy (5–10% of Guillain-Barré syndrome cases)	GM1, GD1a, GD3	50%
Miller Fisher syndrome	GQ1a, GT1a	85%
Ataxic neuropathies (CANOMAD, acute sensory ataxic neuropathy)	GD1b	46%
Distal acquired demyelinating symmetric neuropathy (DADS)	IgM monoclonal protein	Approximately 100%
	MAG	50%
POEMS syndrome	Lambda light chain	85%
Multifocal motor neuropathy (MMN)	IgM GM1	48%
	IgM GM1:GalC	75%
Paraneoplastic sensory neuronopathy	ANNA-1 (Hu)	Approximately 60%
	CRMP-5 (CV-2)	Unknown
Sensory neuronopathy associated with Sjögren syndrome	SSA (Ro), SSB (La)	Approximately 50%
Vasculitic neuropathy associated with:		
Microscopic polyangiitis	ANCA	60–80%
Eosinophilic granulomatosis with polyangiitis	ANCA	30–40%
Granulomatosis with polyangiitis	ANCA	90%

ANCA = antineutrophil cytoplasmic antibody; ANNA-1 = antineuronal nuclear antibody type 1; CANOMAD = chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies; CRMP-5 = collapsin response mediator protein-5; IgM = immunoglobulin M; MAG = myelin-associated glycoprotein; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes; SSA = Sjögren syndrome A; SSB = Sjögren syndrome B.

TABLE 1-12 Disorders for Which Nerve Biopsy Might Be Considered

- ▸ Disorders for which nerve biopsy can be diagnostic where nerve biopsy is endorsed if not readily achieved by less invasive means
  - Vasculitic neuropathy (systemic or nonsystemic)
  - Amyloidosis (primary systemic)
- ▸ Disorders for which nerve biopsy has characteristic or diagnostic features where diagnosis is preferably achieved by less invasive means
  - Amyloidosis (hereditary)
  - Leprosy
  - Sarcoidosis
  - Neurofibromatous neuropathy
  - Neurolymphomatosis
  - Hereditary metabolic/multisystem diseases
    - Fabry disease, metachromatic leukodystrophy, Krabbe disease, adrenomyeloneuropathy, polyglucosan body disease, giant axonal neuropathy, Tangier disease
  - Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), Guillain-Barré syndrome
  - Distal acquired demyelinating symmetric (DADS) neuropathy
  - Hereditary neuropathy with liability to pressure palsies (HNPP)
  - Hexacarbon toxicity
- ▸ Rare conditions for which nerve biopsy has been diagnostic in isolated reports
  - Silver toxicity
  - Hereditary disorders of uric acid metabolism

Continuum (Minneap Minn) 2017;23(5):1241–1262

ACUTE NEUROPATHY

Gullain Barre syndrome
Vasculitic Neuropathy

ALL GBS SPECTRUM DISORDERS

Core features
- Mostly symmetric pattern of limb and/or motor cranial-nerve weakness
- Monophasic disease course with interval between onset and nadir of weakness of 12 h to 28 days, followed by clinical plateau

Note
- Alternative diagnosis should be excluded

Supportive features
- Antecedent infectious symptoms
- Presence of distal paraesthesia at or before the onset of weakness
- Cerebrospinal fluid :albuminocytological dissociation

Wakerley, B. R. *et al. Nat. Rev. Neurol.* advance online publication 29 July 2014;

OPINION

Guillain–Barré and Miller Fisher syndromes—new diagnostic classification

Table 1 | Clinical features of GBS, MFS and their subtypes

Category	Clinical features		
	Pattern of weakness	Ataxia	Hypersomnolence
GBS			
Classic GBS	Four limbs	No or minimal	No
Pharyngeal–cervical–brachial weakness*	Bulbar, cervical and upper limbs	No	No
Acute pharyngeal weakness‡	Bulbar	No	No
Paraparetic GBS*	Lower limbs	No	No
Bifacial weakness with paraesthesias*	Facial	No	No
MFS			
Classic MFS	Ophthalmoplegia	Yes	No
Acute ophthalmoparesis§	Ophthalmoplegia	No	No
Acute ataxic neuropathy‖	No weakness	Yes	No
Acute ptosis§	Ptosis	No	No
Acute mydriasis§	Paralytic mydriasis	No	No
BBE¶	Ophthalmoplegia	Yes	Yes
Acute ataxic hypersomnolence¶	No weakness	Yes	Yes

*Localized subtypes of GBS. ‡Incomplete form of pharyngeal–cervical–brachial weakness. §Incomplete forms of MFS. ‖CNS subtype of MFS. ¶Incomplete form of BBE. Abbreviations: BBE, Bickerstaff brainstem encephalitis; GBS, Guillain–Barré syndrome; MFS, Miller Fisher syndrome.

Wakerley, B. R. *et al. Nat. Rev. Neurol.* advance online publication 29 July 2014;

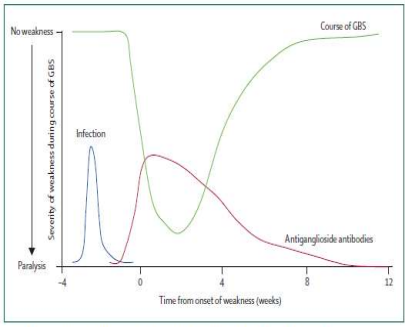
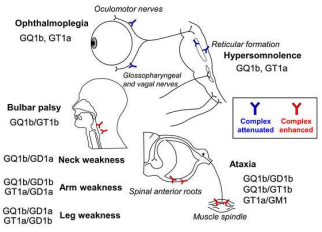


Figure 1: Relation between infections, antiganglioside antibodies, and clinical course of GBS

PROPOSED ANTIGEN DISTRIBUTION



European Journal of Neurology 2015, **0**: 1–7

Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria

Brain 2014: 137; 33–43

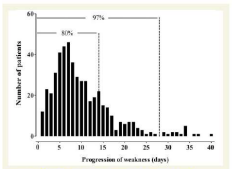


Figure 2 Duration of the progressive phase is defined as the number of days between onset of limb weakness and reaching nadir. The figure shows a skewed distribution in which the duration of the progressive phase is <2 weeks in 80% and <4 weeks in 97% of patients.

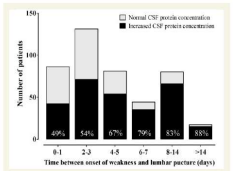
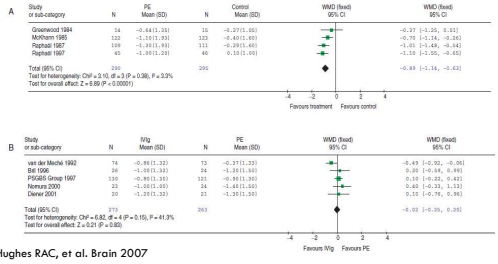


Figure 3 Number of patients and percentages with elevated protein concentration in CSF in relation to the timing of the lumbar puncture after onset of weakness.

FEATURES THAT SHOULD RAISE DOUBT ABOUT THE DIAGNOSIS OF GBS

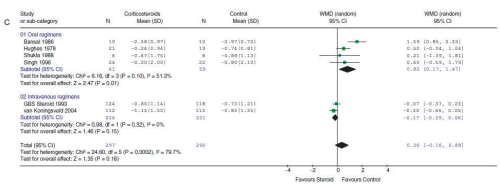
- Increased number of mononuclear cells in cerebrospinal fluid (>50 cells per µl) or PMN cells in cerebrospinal fluid
- Severe pulmonary dysfunction with limited limb weakness at onset
- Severe sensory signs with limited weakness at onset
- Bladder or bowel dysfunction at onset
- Fever at onset
- Sharp spinal cord sensory level
- Slow progression with limited weakness and without respiratory involvement (consider subacute inflammatory demyelinating polyneuropathy or acute-onset chronic inflammatory demyelinating polyneuropathy)
- Marked persistent asymmetry of weakness
- Persistent bladder or bowel dysfunction

A: PE VS CONTROL
B: IVIG VS PE



Hughes RAC, et al. Brain 2007

C: STEROID VS PLACEBO



Hughes RAC, et al. Brain 2007

บัญชียาสำหรับโรงพยาบาลและสถานบริการสาธารณสุข

5.3.2 โรค Guillain–Barré syndrome ที่มีอาการรุนแรง

แนวทางกำกับการใช้ยา

1. ระบบอนุมัติการใช้ยา

เนื่องจากการใช้ IVIG ให้ใช้เฉพาะเมื่อผู้ป่วยมาด้วยภาวะฉุกเฉิน เช่น severe type, progressive weakness หรือมี acute respiratory failure จำเป็นต้องได้รับยาในทันที (ไม่นานเกิน 1-2 วัน) มิเช่นนั้นผู้ป่วยอาจถึงแก่ชีวิตได้ (Life-threatening) จึงควรกำหนดให้ขออนุมัติการใช้ยา IVIG จากหน่วยงานสิทธิประโยชน์ภายหลังการรักษา (post-authorization)

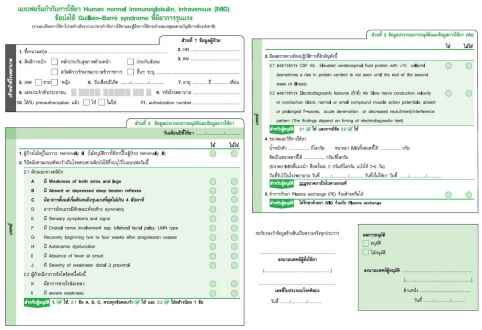
หมายเหตุ ควรมีระบบการอนุมัติการใช้ยาภายในโรงพยาบาล (pre-authorization) เนื่องจากไม่ได้เป็นโรคที่เป็นภาวะฉุกเฉินที่ต้องให้ในทันที อาจรอปรึกษาใน 24-48 ชั่วโมงก่อนได้

6. ขนาดยาที่แนะนำ และวิธีการให้ยา

ขนาดยาที่แนะนำ คือ 2 กรัมต่อน้ำหนักตัว 1 กิโลกรัมต่อการรับไว้ในโรงพยาบาล 1 ครั้ง แบ่งให้ 2-5 วัน (เช่น 0.4 กรัมต่อน้ำหนักตัว 1 กิโลกรัมต่อวัน นาน 5 วัน) ให้ยาด้วยวิธี continuous drip และต้องได้รับ IVIG ภายใน 2 สัปดาห์หลังจากเริ่มมีอาการทางคลินิก

7. ข้อสังเกต

- ประสิทธิผลของ IVIG เทียบเท่ากับ plasma exchange
- การให้สเตียรอยด์ ร่วมกับ IVIG หรือ plasma exchange พบว่าไม่มีประโยชน์
- การให้ IVIG ร่วมกับ plasma exchange พบว่าไม่มีประโยชน์มากกว่าอย่างใดอย่างหนึ่งเพียงอย่างเดียว



Outcome of Guillain Barré syndrome in Thailand

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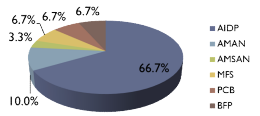
© 2015 European Journal of Neurology, 22 (Suppl. 1), 484–828

Nationality

GBS subtypes



(J Clin Neuromusc Dis 2017;19:51-56)

Predictors of inability to walk unaided (GBS disability score ≥ 3)

	rs	p value
Older age	0.428	0.018**
Previous diarrhoea	0.398	0.029*
Autonomic disturbances	0.438	0.015**
Distal upper limbs weakness	0.362	0.049*
Proximal lower limbs weakness	0.446	0.014**
Distal lower limbs weakness	0.378	0.040*
Facial weakness	-0.453	0.012**
Bulbar weakness	-0.393	0.032*
Higher disability score at admission	0.367	0.046*
Higher disability score at treatment onset	0.396	0.030*

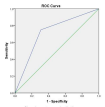
*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

Modified Erasmus GBS Outcome Scores[1]

Prognostic factors	Score
Age at onset, y	
>40	0
41-60	1
>60	2
Preceding diarrhea*	
Absent	0
Present	1
MRC sumscore (at hospital admission)	
51-60	0
41-50	2
31-40	4
0-30	6
mEGOS	0-9

†Adapt from Walgaard et al.(2011)

AUC-ROC Curve for mEGOS at admission
(optimal cut-off= 4; AUC 0.72)



CHRONIC POLYNEUROPATHY

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of laboratory and genetic testing (an evidence-based review)

Hematology –
- complete blood count,
- erythrocyte sedimentation rate or C-reactive protein,
- vitamin B-12*, folate.
- Methylmalonic acid with or without homocysteine for low normal vitamin B-12 levels*

Urine –
- urinalysis,
- urine protein electrophoresis with immunofixation

Drugs and Toxins –
- Inquire about drugs and toxins

Biochemical and endocrine
- comprehensive metabolic panel
  - fasting blood glucose*
  - renal function
  - liver function),
- thyroid function tests.
- Serum protein immunofixation electrophoresis*.

Glucose tolerance test if indicated to look for impaired glucose tolerance*.

*Tests with the highest yield (Class III).
Neurology© 2009;72:185-192

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of laboratory and genetic testing (an evidence-based review)

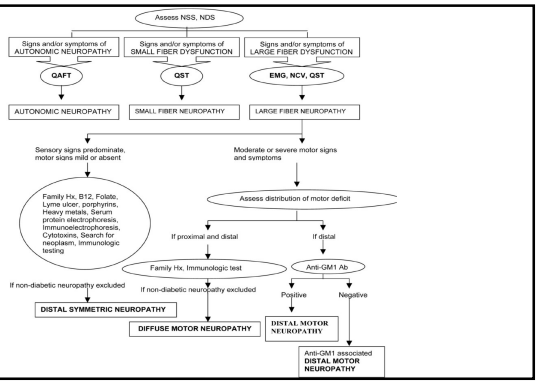
Neurology© 2009;72:185-192

Screening laboratory tests may be considered for all patients with DSP (Level C)

The highest yield of abnormality are blood glucose, serum B12 with metabolites (methylmalonic acid with or without homocysteine), and serum protein immunofixation electrophoresis (Level C).

When routine blood glucose testing is not clearly abnormal, other tests for prediabetes such as a GTT may be considered in patients with DSP, esp with pain (Level C).

Impaired fasting glucose is defined as a plasma glucose level greater than 100 and less than 126 mg/dL; impaired glucose tolerance as a 2-hour glucose level between 140 and 199 mg/dL after a 75-g oral glucose load (GTT).



SPECIAL ARTICLE
AMERICAN ACADEMY OF NEUROLOGY

Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review)

Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation

1) Autonomic testing should be considered in the evaluation of patients with polyneuropathy to document autonomic nervous system dysfunction (Level B)

- Such testing should be considered especially for the evaluation of suspected autonomic neuropathy (Level B) and distal small fiber sensory polyneuropathy (SFSN) (Level C).
- A battery of validated tests is recommended to achieve the highest diagnostic accuracy (Level B).

SPECIAL ARTICLE
AMERICAN ACADEMY OF NEUROLOGY
Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review)
Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation

2) Nerve biopsy is generally accepted as useful in the evaluation of certain neuropathies as in patients with suspected amyloid neuropathy, mononeuropathy multiplex due to vasculitis, or with atypical forms CIDP.

However, the literature is insufficient to provide a recommendation regarding when a nerve biopsy may be useful in the evaluation of DSP (Level U).

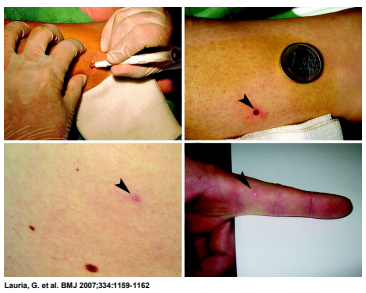
SPECIAL ARTICLE
AMERICAN ACADEMY OF NEUROLOGY
Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review)
Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation

3) Skin biopsy is a validated technique for determining intraepidermal nerve fiber density and may be considered for the diagnosis of DSP, particularly SFSN (Level C).

There is a need for additional prospective studies to define more exact guidelines for the evaluation of polyneuropathy.

Neurology 2009; 72:1-1

Fig 3 Skin biopsy performed using a 3 mm disposable punch (top left). Healed biopsy site (arrowhead; top right). Scar on hairy skin three months after biopsy (arrowhead; bottom left). Scar on glabrous skin eight weeks after biopsy (arrowhead; bottom right)

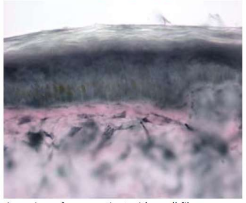


Lauria, G. et al. BMJ 2007;334:1159-1162

Normal skin biopsy

Normal innervation with small nerve fibers seen in the epidermis (arrows). Skin biopsy specimens with protein gene product 9.5 immunostaining.

Small fiber neuropathy biopsy



A specimen from a patient with small fiber neuropathy shows denervation with no small nerve fibers seen in the epidermis.

THE TWO MAJOR TYPES OF NEUROPATHY

Axonal type
Demyelinating type

DIFFERENTIAL DIAGNOSIS

Box 1 Commonest causes of chronic axonal neuropathy

- Diabetes mellitus
- Alcohol
- Uraemia
- Cirrhosis
- Amyloidosis due to plasma cell dyscrasia, and in amyloidosis with myeloma (light chain amyloidosis)
- Myxoedema
- Acromegaly
- Toxins (box 2)
- Drugs (table 2)
- Deficiency diseases (table 3)
- Paraneoplastic
- Hereditary
- Infection: leprosy, HIV
- Idiopathic

Box 3 Causes of chronic demyelinating neuropathy

Chronic inflammatory demyelinating polyradiculo-neuropathy:
- Typical symmetrical
- Multifocal acquired demyelinating sensory and motor neuropathy
- symmetrical motor
- symmetrical sensory

Multifocal motor neuropathy
Paraprotein associated demyelinating neuropathy
Charcot-Marie-Tooth disease type 1 and type X

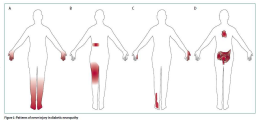
2008;**8**:396–405. doi:10.1136/jnnp.2008.162412

CLASSIFICATION OF DIABETIC NEUROPATHY

Somatic neuropathies
- Mononeuropathy: median, CN III, VII
- Polyradiculopathy: lumbosacral
- Mononeuritis multiplex
- Symmetric sensory polyneuropathy

Small fiber neuropathy

Autonomic neuropathy



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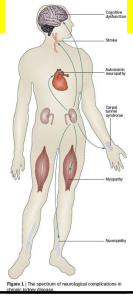
NOT ALL NEUROPATHY IN DIABETES IS OF DIABETIC ETIOLOGY

10% to 50% of DM may have an additional potential cause of a peripheral neuropathy

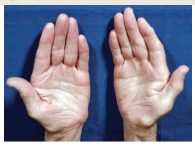
Some may have more than one cause.

Differential diagnosis
- Neurotoxic medications
- Alcohol abuse
- Vitamin deficiency (B1, B12)
- Uremia
- CIDP
- Inherited neuropathy
- Vasculitis

CHRONIC KIDNEY DISEASE (UREMIA)



Box 2 | Proposed criteria for a uremic neurotoxin
- Must be an identifiable chemical
- Should be elevated in the blood of patients with uremia
- A direct positive relationship should exist between blood level and neurological dysfunction
- Should cause neurological dysfunction in experimental animals at appropriate blood levels
- Removal from the blood should abolish the neurological dysfunction



Nat. Rev. Neurol. **5**, 542–551 (2009)

Table 1 | Neurological disorders in patients with CKD

Neurological disorder	Prevalence	Clinical features	Management
Cognitive dysfunction	30–40% of patients on dialysis	Impairments in memory and executive function	Most effective: renal transplantation Other option: erythropoietin
Restless legs syndrome	15–20% of patients with CKD	Subjective urge to move the legs, worse nocturnally; symptoms exacerbated by inactivity and relieved by movement	Most effective: dopaminergic agonists; levodopa Other option: advice regarding sleep hygiene
Length-dependent uremic neuropathy	90% of patients with CKD	Sensory loss, weakness and wasting, maximal distally; absence of ankle jerks; lower limbs more severely affected than upper limbs	Most effective: transplantation, adequate dialysis (increase frequency or use high-flux dialysis); neuropathic pain therapy Other options: vitamin supplementation; strict potassium restriction; erythropoietin; exercise program
Autonomic neuropathy	~60% of patients with CKD	Impotence; postural hypotension; cardiac arrhythmia; symptomatic intradialytic hypotension	Most effective: transplantation; adequate dialysis; sildenafil to treat impotence Other option: midodrine to treat intradialytic hypotension
Carpal tunnel syndrome	5–30% of patients with CKD	Hand paresthesia and numbness; weak thumb abduction	Most effective: splinting; local steroid injection; surgical decompression
Ischemic monomelic neuropathy	Rare in CKD	Diffuse weakness and sensory loss distal to an arteriovenous fistula	Immediate fistula banding or ligation
Uremic myopathy	50% of patients with CKD	Proximal weakness of the lower limbs	Most effective: adequate dialysis; exercise program; adequate nutrition Other options: erythropoietin; L-carnitine

UREMIC NEUROPATHY

Typical sensorimotor axonal polyneuropathy

- Direct correlation with declining GFR (<12)
- Large and small fiber features

Axonal shrinking and fiber loss, secondary demyelination

QST: reduced vibration and thermal but increase heat and cold perception

Coexisting cramps, restless leg, prutitus, ANS dysfunction, rare GBS-like

Pathophysiology

- Neurotoxic middle molecules vs
- hyperkalemia induced persistent depolarization

ENVIRONMENTAL TOXIN

Box 2 Industrial and environmental toxins which cause peripheral neuropathy

- Acrylamide
- Arsenic
- Lead
- Mercury
- Thallium
- Organophosphates
- Carbon disulphide
- Organic solvents: *n*-hexane and methyl-*n*-butyl ketone

Metal toxicity

- Chronic arsenic: painful length dependent neuropathy, hyperpigmentaion, Mees lines
- Lead: motor dysfunction in upper limb,
  - Common features: radial neuropathy
  - Weight loss, fatigue, abdominal pain, Lead lines at gum
- Thallium: rodenticide, pesticide
- Mercury: mutisystem features

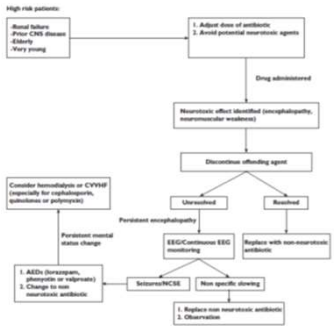
Hexacarbon

- Distal sensorimotor polyneuropathy
- Classic axonal swelling, neurofilamentous aggregates

Acrylamide

- Large fiber neuropathy, areflexia
- Interference with axonal transport mechanism

ANTIBIOTIC NEUROTOXICITY



EXAMPLE OF DRUG INDUCED NEUROPATHY

Anti-infectious medications
- Chloroquine
- Dapsone
- Isoniazid
- Metronidazole
- Nitrofurantoin

Dideoxycytidine and other nucleoside analogs
- Quinolones
- Polymyxin B, Colistin
- Tetracycline

Antirheumatic and immunosuppressants
- Chloroquine
- Colchicine

Cardiovascular medications
- Amiodarone
- Hydralazine
- Perhexiline
- Propafenone

Psychiatric and sedatives
- Disulfiram

Other medications
- Pyridoxine (vitamin B6)
- Phenytoin

Chemotherapy and anticancer medications
- Cisplatinum
- Taxanes (paclitaxel and docetaxel)
- Suramin
- Thalidomide
- Vincristine
- Bortezomib

ALCOHOL NEUROPATHY

Pure alcohol neuropathy, without B1 deficiency is a sensory-dominant and slowly progressive PN

Burning pain: initial and most troublesome symptom

The disorder progresses gradually over years.

Vagal dysfunction may be present and has been associated with a poor prognosis

Nociceptive impairment on examination

Nerve biopsy reveals a reduction in small myelinated and unmyelinated fibers

Neurotoxic effect: axonal degeneration

NUTRITIONAL DEFICIENCY

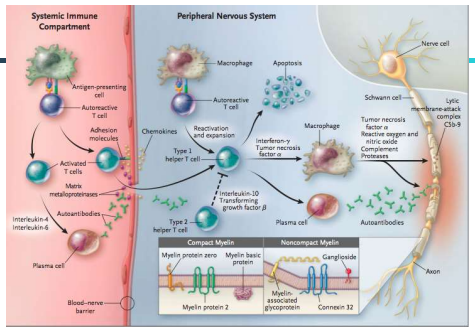
Table 3 Deficiencies which cause peripheral neuropathy

Thiamine	In malnourished, alcohol abuse and after gastric surgery
Pyridoxine	Overdose also causes neuropathy
Vitamin E	May be associated with cerebellar syndrome
Vitamin B_{12}	Predominantly sensory, with spinal cord involvement
Strachan's syndrome	Painful sensory neuropathy, optic neuropathy and deafness, in association with orogenital dermatitis: reported from tropical countries
Coeliac disease	Controversial whether coeliac disease causes neuropathy in the absence of vitamin deficiency

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

CIDP KEY FEATURES

- Progression over at least two months
- Weakness more than sensory symptoms
- Symmetric involvement of arms and legs
- Proximal muscles involved along with distal muscles
- Reduced deep tendon reflexes throughout
- Increased cerebrospinal fluid protein without pleocytosis
- Nerve conduction evidence of a demyelinating neuropathy
- Nerve biopsy evidence of segmental demyelination with or without inflammation



PATHOLOGY

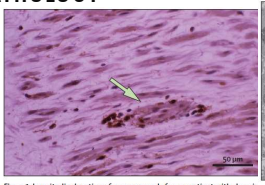


Figure 1: Longitudinal section of a nerve sample from a patient with chronic inflammatory demyelinating polyradiculoneuropathy
Immunostaining for macrophages (anti-CD68). Several inflammatory cells surround an endoneural capillary.

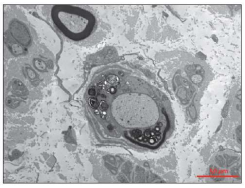


Figure 2: Transverse section of a nerve sample from a patient with chronic inflammatory demyelinating polyradiculoneuropathy
A macrophage loaded with myelin debris has penetrated the cytoplasm of a Schwann cell whose myelin sheath has almost completely disappeared so that the axon seems totally demyelinated.

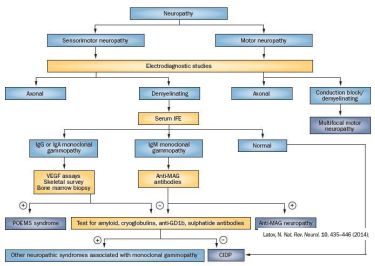
Table 2 | Characteristic abnormalities found in different diagnostic tests

Neuropathy	Electrodiagnostic tests	Serological tests	Nerve biopsy
Chronic inflammatory demyelinating polyneuropathy (CIDP)	Multifocal demyelinating abnormalities	None	Segmental demyelination and remyelination Loss of large myelinated axons 'Onion bulbs'
Anti-MAG neuropathy	Disproportionate prolongation of distal latencies	IgM monoclonal gammopathy Elevated titres of anti-MAG/SGPG antibodies	Demyelination with loss of large myelinated axons Separation of the myelin lamellae at the minor dense line Deposits of IgM and C3d on myelin sheaths
Multifocal motor neuropathy	Multifocal motor conduction block	Elevated anti-GM1 ganglioside antibodies (50% of cases)	Axonal degeneration Regenerative axonal clusters in motor nerves
POEMS syndrome	Uniform demyelinating changes	λ light chain IgG or IgA monoclonal gammopathy Elevated vascular endothelial growth factor levels	Demyelination with loss of large myelinated axons Separation of the myelin lamellae at the major dense line

Abbreviations: MAG, myelin-associated glycoprotein; SGPG, sulphated glucuronyl paragloboside.

Latov, N. *Nat. Rev. Neurol.* **10**, 435–446 (2014)

DIAGNOSTIC PATHWAY



Latov, N. *Nat. Rev. Neurol.* **10**, 435–446 (2014)

INVESTIGATIONS

Table 2 Investigations to be considered

To diagnose chronic inflammatory demyelinating polyradiculoneuropathy	(b) Studies to be performed if clinically indicated
Electrodiagnostic studies including sensory and motor nerve conduction studies, which may be repeated, performed bilatera or use proximal stimulation for motor nerves	*Skeletal survey Oral glucose tolerance test Borrelia burgdorferi serology C reactive protein Extractable nuclear antigen antibodies Chest radiograph Angiotensin-converting enzyme HIV antibody
CSF examination including cells and protein	
MRI spinal roots, brachial plexus, and lumbosacral plexus	
Nerve biopsy	
To detect concomitant diseases	To detect hereditary neuropathy
(a) Recommended studies	Examination of parents and siblings
*Serum and urine paraprotein detection by immunofixation	Appropriate gene testing (especially PMP22 duplication and connexin 32 mutations)
Fasting blood glucose	Nerve biopsy
Complete blood count	
Renal function	
Liver function	
Antinuclear factor	
Thyroid function	

*Repeating these should be considered in patients who are or become unresponsive to treatment.

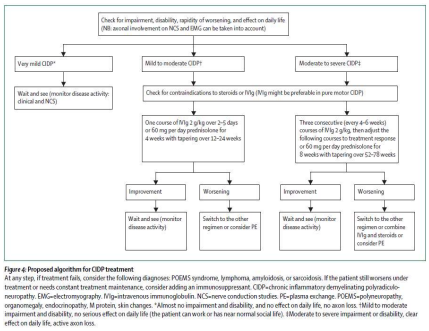


Figure 4: **Proposed algorithm for CIDP treatment**
At any step, if treatment fails, consider the following diagnoses: POEMS syndrome, lymphoma, amyloidosis, or sarcoidosis. If the patient still worsens under treatment or needs constant treatment maintenance, consider adding an immunosuppressant. CIDP=chronic inflammatory demyelinating polyradiculoneuropathy. EMG=electromyography. IVIg=intravenous immunoglobulin. NCS=nerve conduction studies. PE=plasma exchange. POEMS=polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes. *Almost no impairment and disability, and no effect on daily life, no axon loss. †Mild to moderate impairment and disability, no serious effect on daily life (the patient can work or has near normal social life). ‡Moderate to severe impairment or disability, clear effect on daily life, active axon loss.

CASE ILLUSTRATION: WEAK AND NUMBNESS, BUT NO PAIN

Pract Neurol 2007; 7: 93–105

CLUES FOR HEREDITARY NEUROPATHY

Foot deformity such as pes cavus in an adult

No definite sensory symptoms but clear sensory signs.

In the demyelinating forms of CMT (CMT1), neurophysiology can be very useful in distinguishing hereditary from acquired neuropathies

- motor conduction velocities
  - usually uniformly slow in the common hereditary neuropathies
  - patchy slowing in the acquired neuropathies, such as CIDP

TABLE 1 Classification of the inherited neuropathies

Neuropathies in which the neuropathy is the sole or primary part of the disease
- Charcot-Marie-Tooth disease
- Hereditary neuropathy with liability to pressure palsies
- Hereditary sensory and autonomic neuropathies
- Distal hereditary motor neuropathies
- Hereditary neuralgic amyotrophy
- Familial amyloid polyneuropathy

Neuropathies in which the neuropathy is part of a more widespread neurological or multisystem disorder
- Disturbances of lipid metabolism
  - Leukodystrophies
  - Lipoprotein deficiences
  - Phytanic acid storage diseases
  - α galactosidase deficiency
  - Cholestanolosis
  - Sphingomyelin lipidoses
- Porphyrias
  - Acute intermittent
  - Hereditary coproporphyria
  - Variegate
  - ALA dehydrase deficiency
- Disorders with defective DNA
  - Ataxia telangiectasia
  - Xeroderma pigmentosum
  - Cockayne syndrome
- Neuropathies associated with mitochondrial diseases
- Neuropathies associated with hereditary ataxias
  - Friedreich's ataxia
  - Spinocerebellar ataxias
- Miscellaneous
  - Neuroacanthocytosis

HEREDITARY NEUROPATHY