Practical Approach to PeripheralNeuropathy

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INTRODUCTION

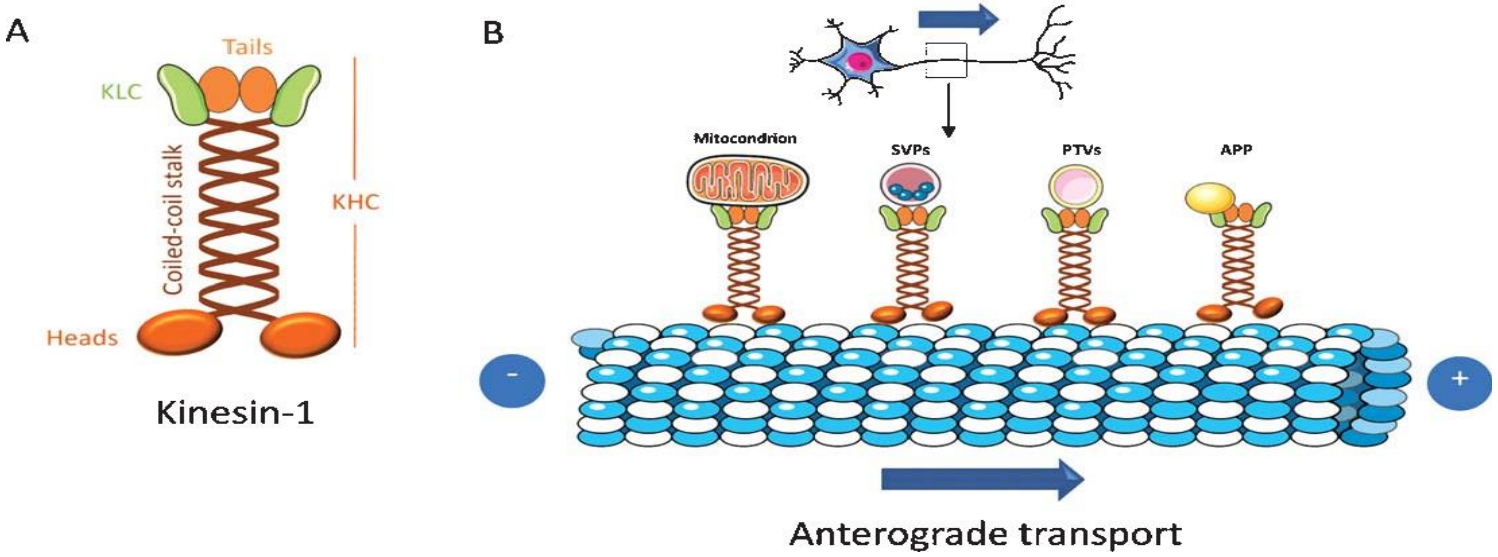
- Peripheral neuropathy is a common neurologic problem.
- approximately 5% of adults and as many as 30% of patients who are elderly.
- In the Netherlands, neuropathy incidence in an adult population approximates 77 per 100,000 person-years.
- incidence and prevalence of neuropathy increase with age.

- The etiologies of peripheral neuropathy are exceeding 200 depending on the classification.
- Although the primary goal in the evaluation of a patient with peripheral neuropathy is to identify the cause whenever possible, a common category of polyneuropathy is chronic idiopathic axonal polyneuropathy close to a half of patients with neuropathy.
- Accurate diagnosis of polyneuropathy directs treatment in a limited number of cases but also provides the benefit of diagnostic closure.

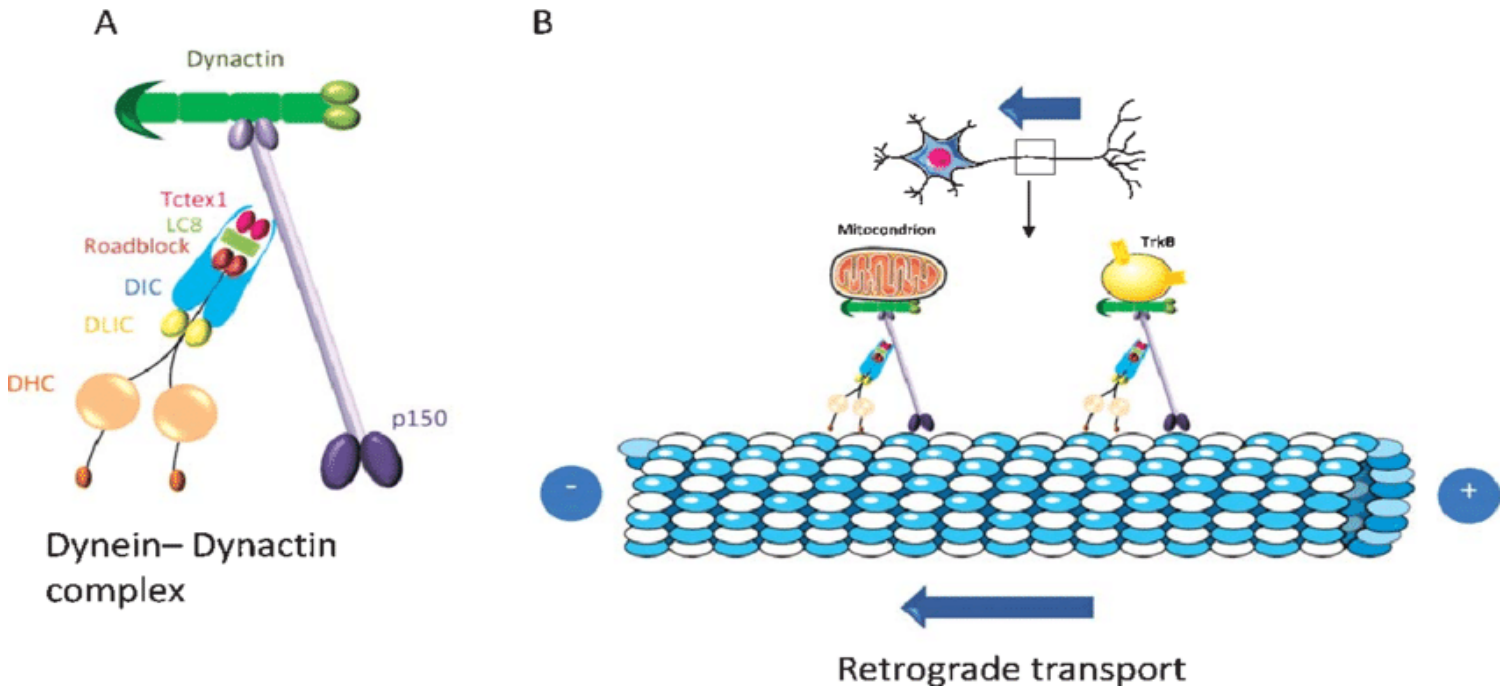
ANATOMIC, PHYSIOLOGIC, AND PATHOPHYSIOLOGIC CONSIDERATIONS IN PERIPHERAL NEUROPATHY

Axonal Polyneuropathies

- Anterograde transport from cell body along axons is dependent on the kinesin family .



- Retrograde transport depends on the dynein/dynactin complex.



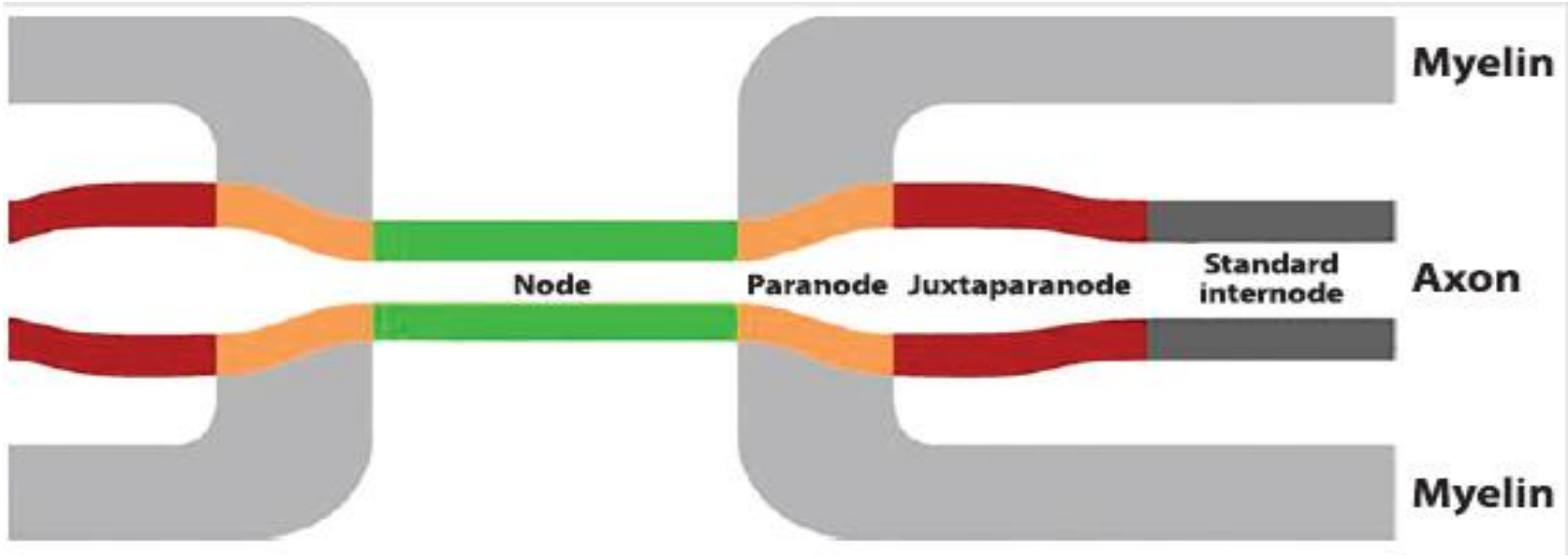
- Disordered axonal transport is thought to be the mechanism underlying the pathophysiology of most toxic and metabolic neuropathies and some hereditary neuropathies.

Demyelinating Polyneuropathies

- Peripheral nerve myelin of Schwann cell origin is compacted along the internode, non compacted at the paranode (allowing for increased surface area of potential pathogenic significance) , and absent at the nodes of Ranvier.
- *May be either acquired or heritable*.

- Charcot-Marie-Tooth disease type 1
- Charcot-Marie-Tooth disease type 3
- Charcot-Marie-Tooth disease type 4
- Hereditary neuropathy with liability to pressure palsies (HNPP)
- Krabbe disease
- Metachromatic leukodystrophy
- Refsum disease
- Cockayne syndrome
- Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome
- Multifocal motor neuropathy (MMN)
- Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)
- Distal acquired demyelinating symmetric neuropathy (DADS)
- Toxins (diphtheria, buckthorn, amiodarone, n-hexane, arsenic)

- Acquired demyelinating neuropathies are thought to be immune mediated through either cellular or humoral mechanisms.
- Antigenic targets are located in the paranodal or juxtaparanodal regions.



- Identifiable autoantibodies in some of these disorders have diagnostic or, in some cases, probable pathogenic relevance.

- Serves to justify immunomodulating treatment in certain syndromes.

- Autoantibodies directed against GM1, GD1a, and GT1b affect motor nerves, GD1b autoantibodies target sensory nerves, GQ1b autoantibodies are concentrated in the paranodal regions of cranial nerves III, IV, and VI.

- The blood-nerve barrier is less well established at the nerve roots, dorsal root ganglia, and terminal nerve twigs.
- These regions are often preferentially involved in the inflammatory/ immune polyradiculoneuropathies.

Nodopathies (Channelopathies)

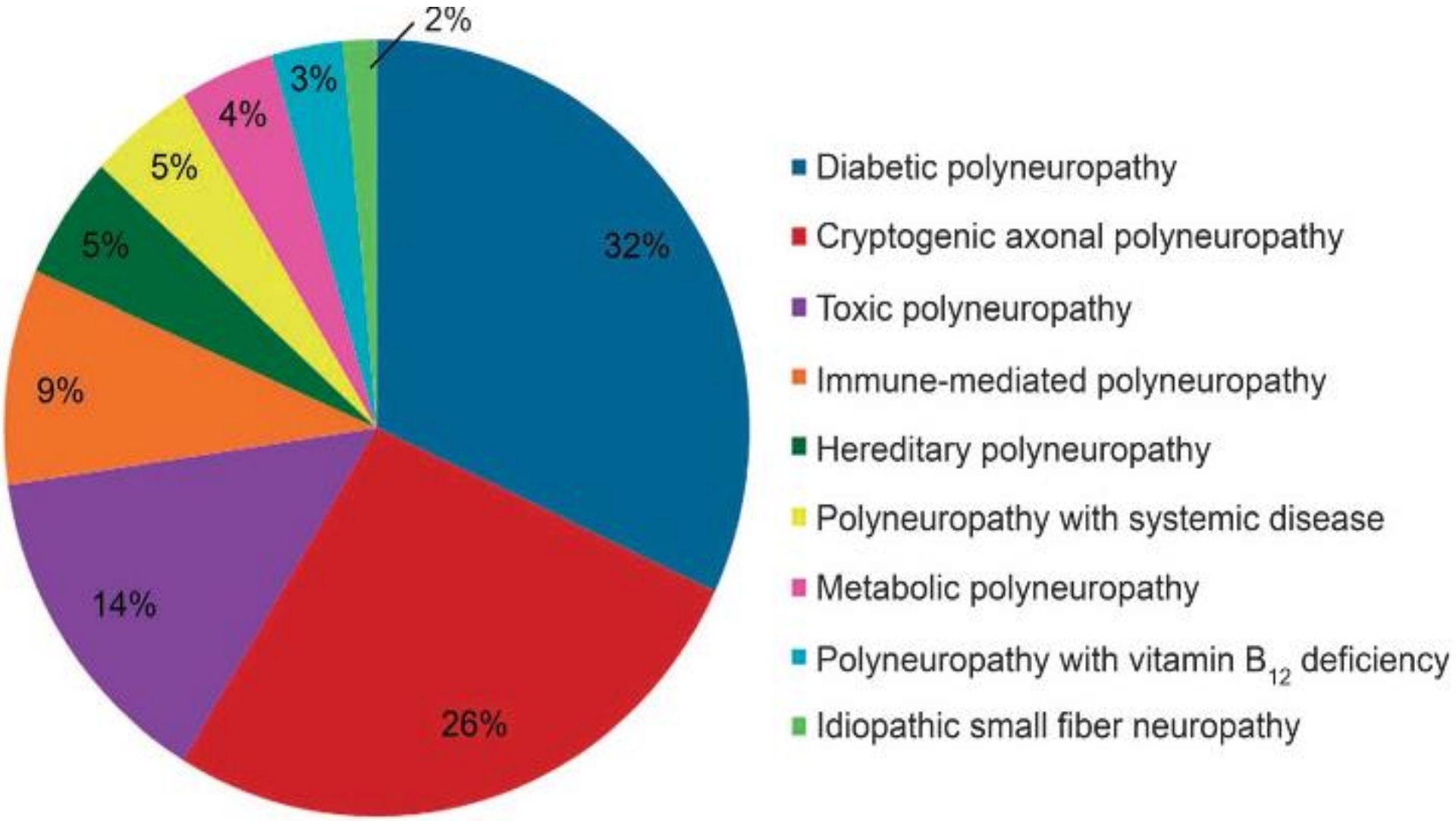
- Some toxic, immunemediated, and hereditary disorders target proteins and ion channels in the nodal region.
- Characterized by rapid decline of compoun muscle action potential (CMAP) amplitudes, suggesting motor axon loss.
- Rapid resolution of clinical and nerve conduction study changes.

AMAN is frequently associated with autoantibodies directed against GM1 and GD1a gangliosides, localized on the nodal axolemma.

Nodopathies
Acute motor axonal variant of Guillain-Barre´ syndrome
(CIDP) associated with autoantibodies to nodal antigens
Miller Fisher syndrome
Multifocal motor neuropathy (MMN)
Marine toxins (saxitoxin, ciguatoxin, tetrodotoxin)
Drugs with ion channel blocking properties (phenytoin)
Possibly critical illness polyneuropathy
Possibly ischemic monomelic neuropathy
Possibly thiamine deficiency

CLASSIFICATION AND CAUSES OF POLYNEUROPATHIES

- Based on the initial location of pathology.
- Neuropathies that appear to originate in motor or sensory cell bodies are referred to as neuronopathies.
- The primary benefit of neuropathy classification is to limit differential diagnostic considerations in order to generate a rational and targeted diagnostic strategy.


2%
3%
4%
5%
5%
9%
14%
26%
32%
Diabetic polyneuropathy
Cryptogenic axonal polyneuropathy
Toxic polyneuropathy
Immune-mediated polyneuropathy
Hereditary polyneuropathy
Polyneuropathy with systemic disease
Metabolic polyneuropathy
Polyneuropathy with vitamin B_{12} deficiency
Idiopathic small fiber neuropathy

- In addition to primary anatomic target (axon or myelin), neuropathy pattern (length dependent or non-length dependent), or size of peripheral nerve fibers (ie, small or large) should be cosederd.

Length-dependent Neuropathies

- large fiber sensory

  - Numbness or loss of sensation and liken it to a sense of swelling or feeling as though their socks.

  - loss of balance may be described.

  - In hereditary neuropathies, the patient may not be aware.

Common Causes of Length-dependent Polyneuropathy

Category	Notable Examples	Estimated Prevalence of All Types
Diabetes mellitus	Large fiber sensory predominant	33%
	Small fiber	10–25% of above
	Impaired glucose tolerance	Unknown
Chronic idiopathic axonal polyneuropathy	Idiopathic	25–55%
Small fiber neuropathy	Idiopathic	2%
Hereditary	Charcot-Marie-Tooth disease (hereditary motor sensory neuropathy), hereditary sensory and autonomic neuropathy, hereditary motor neuropathy	5–33%
Metabolic	Vitamin B_{12}/other nutritional deficiency, end organ failure/critical illness polyneuropathy	12%
Toxic	Chemotherapy, industrial/ environmental toxins	14%
Inflammatory	Distal acquired demyelinating symmetric neuropathy associated with IgM monoclonal protein	9%

- one-third of these patients are estimated to have neuropathic pain, suggesting that certain neuropathies have large and small fiber overlap.
- Ankle muscle stretch reflexes may be diminished or absent , but other reflexes are typically initially preserved.
- A multifocal neuropathy may be mistaken for Length-dependent

❖Small Fiber Polyneuropathy

- painful dysesthetic sensations, such as burning or localied shooting pains, and may experience dysautonomia.

- Diagnostic criteria :1- Probable

I. distal symmetric polyneuropathy.

II. normal sural sensory nerve action potential (SNAP).

2- Definite either an abnormal intraepidermal nerve fiber density OR abnormal thermal response to quantitative sensory testing.

- Small fiber neuropathies have subcategory of painful length-dependent neuropathies, but one-fourth to a one-third may be non-length based.
- Length-dependent presentations demyelinating neuropathies ; ataxic sensory neuropathy associated with IgM monoclonal proteins related, in many cases, with MAG autoantibodies.

- patients with a length-dependent pattern with motor predominance, CMT, hereditary motor neuropathies, and distal myopathies should be considered.
- Preservation of toe extension relative to foot dorsiflexion is one clue suggesting myopathy.

Non length-dependent Neuropathies

- Non length-dependent polyneuropathies include neuronopathies, multifocal neuropathies, polyradiculopathies, and polyradiculoneuropathies.
- Demyelinating characteristics include MMN, MADSAM, hereditary neuropathy with liability to pressure palsies (HNPP), and CMT type X in some cases.

Polyradiculopathies :Acquired

Structural	Spondyloarthropathy Spinal stenosis
Radiation	
Neoplastic	Non-Hodgkin lymphoma Acute leukemia Melanoma Carcinoma
Infectious	Lyme disease Cytomegalovirus HIV Tuberculosis
Inflammatory	Sarcoidosis

Polyradiculoneuropathy

Hereditary	Porphyria
Inflammatory	GBS CIDP POEMS
Toxic	Arsenic n-Hexane Amiodarone
Metabolic/Ischemic	Diabetic radiculoplexus neuropathy
Idiopathic	Idiopathic radiculoplexus neuropathy

DIAGNOSTIC TESTING STRATEGIES

Electrodiagnostic Testing

- AAN practice parameter endorses the use of electrodiagnostic testing in patients with suspected neuropathy.
- Patients with long-standing symptoms and minimal morbidity do not need electrodiagnostic testing unless results are likely to influence diagnosis and treatment.
- EMG: foot muscles are the most likely place to find early abnormalities, denervation potentials indicate motor involvement. BE CAREFUL

Blood and Cerebrospinal Fluid Testing

- AAN guidelines: vitamin B12, methylmalonic acid, and glucose levels and serum protein immunofixation in patients with distal symmetric polyneuropathy patterns.
- Additional testing should be considered:

1. **Acute to subacute onset**
2. **Rapid progression**
3. **Motor predominance**
4. **Non-length dependence**
5. **Associated dysautonomia**
6. **Associated systemic disease**

CSF analysis:

- Not routinely recommended.
- should be considered with a polyradiculopathy or polyradiculoneuropathy pattern.

Antibody Testing

The use of autoantibody panels should be avoided.

Significant false-positive results.

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 polyangitiis	ANCA	30–40%
Granulomatosis with polyangiitis	ANCA	90%

Genetic Testing

- Professional neurologic associations recognize the value of genetic testing in the evaluation of neuropathy when used in a judicious and targeted fashion.
- In studies of middle-aged to elderly patients with neuropathy, hereditary causes have been estimated to represent as little as 0.3% to 3% of the neuropathy cohort.

- The majority of hereditary neuropathies fall into the CMT category.
- The majority of patients with a CMT phenotype have one of four mutation.
- Targeted strategy of discriminant single-gene testing limited to these four genes and refined by considerations of onset age and nerve conduction velocity.

- initially test for the peripheral myelin protein PMP22 deletion/ duplication in an individual with demyelinating conduction velocities.
- next-generation sequencing is recommended in those individuals with negative PMP22 analysis or in patients with unexplained chronic neuropathy who are younger than 40 years of age, have a motor predominant pattern, or have other similarly affected family members.

Histologic Testing

- Peripheral nerve biopsy remains a valuable tool in a very select group of individuals whose pattern suggests a cause for which biopsy diagnosis that cannot be confirmed with less invasive means.
- Assessment of epidermal nerve fiber density through skin biopsy is useful in support of a diagnosis of small fiber neuropathy but rarely identifies the underlying cause.

Disorders for Which Nerve Biopsy Might Be Considered

I. Vasculitic neuropathy
II. Amyloidosis
III. Leprosy
IV. Sarcoidosis
V. Neurofibromatous neuropathy
VI. Neurolymphomatosis
VII. Hereditary metabolic/multisystem diseases : Fabry disease, metachromatic leukodystrophy, Krabbe disease
VIII. CIDP
IX. DADS
X. NHPP

CONCLUSION

10 STEPS IN CHARACTERIZING AND DIAGNOSING PATIENTS WITH PN

1. *Characterize the anatomic-pathologic pattern of involvement.*
2. *Confirm the inferred anatomic-pathologic pattern by use of characterizing tests.*
3. *Infer the pathologic site and mechanism of nerve fiber alterations.*
4. *Consider the onset and course of neuroprithy.*
5. *Decide whether the disorder is likely to be inherited or acquired.*
6. *Check for associations with present or past diseases.*
7. *Perform hematologic, biochemical, serologic, imaging, and other tests.*
8. *Evaluate kin.*
9. *Perform a cutaneous or nerve biopsy.*
10. *Perform a therapeutic trial.*

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