The Evaluation of Polyneuropathies

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Polyneuropathy has an estimated prevalence of 2%–3% in the general population and a prevalence as high as 8% in people over the age of 55 years.¹ Roughly one-third of polyneuropathies will have a genetic cause, one-third an acquired etiology, and one-third will be idiopathic, despite appropriate diagnostic evaluation.² There are over 100 known acquired and inherited disorders that may cause polyneuropathy, a fact that presents challenges and can contribute to uncertainty about the scope, direction, and level of aggressiveness of any evaluation.³ This sometimes leads to a

one-size-fits-all diagnostic strategy, a strategy that is unfocused, inefficient, and costly, and sometimes places the patient at unnecessary risk of a procedure-related complication (e.g., nerve biopsy).

In this article, we present a simple and easy-to-remember algorithm for diagnosing polyneuropathy, based on first answering 4 clinical questions: what, where, when, and what setting (figure 1).³ The 4-step clinical characterization should almost always be followed by electrodiagnostic (EDX) characterization with appropriate nerve conduction and needle EMG. The clinical and EDX characterization can then be combined, as necessary, with a consultation of appropriate tables and lists of differentials or the figure we provide in this article, allowing for the generation of a focused differential diagnosis and appropriate and efficient evaluation.

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CLINICAL APPROACH TO NEUROPATHY What?

The question “what?” refers to which nerve fiber modalities (sensory, motor, autonomic, or a combination) are involved. Identification of sensory nerve involvement allows the clinician to exclude from consideration

“Most patients with polyneuropathy have some degree of motor nerve involvement—especially distally on examination or on EDX testing—that is sometimes overshadowed by sensory complaints”

neuromuscular diseases not associated with sensory dysfunction, such as myopathies, neuromuscular transmission disorders, or disease of the anterior horn cell (e.g., amyotrophic lateral sclerosis). When sensory features are present, the characterization of sensory symptoms as being positive or negative can be helpful because most acquired neuropathies are accompanied by positive neuropathic sensory symptoms (P-NSS) and most inherited polyneuropathies are not. P-NSS may be painful (“electric shock,” “burning,” “throbbing”) or painless (“tingling,” “swelling,” “bunched-up socks”). Most patients with polyneuropathy have some degree of

motor nerve involvement—especially distally on examination or on EDX testing—that is sometimes overshadowed by sensory complaints. Symptoms suggesting autonomic nerve involvement, especially gastrointestinal (e.g., early satiety, constipation), cardiovascular (e.g., orthostatic symptoms), and pupillomotor (e.g., Adie pupil), can be important clues because the numbers of processes that cause clinically meaningful somatic plus autonomic polyneuropathy are relatively few and especially important to diagnose (table 1).^{4,5}

Where? “Where?” refers to the distribution of nerve involvement in terms of 1) the global distribution throughout the body and 2) the distribution of involvement along the nerves. It is important to determine whether a neuropathic process is length-dependent (e.g., distal) or not. Length-dependent polyneuropathies are common and often manifest symmetrically. In contrast, patients with non-length-dependent polyneuropathies might complain of proximal sensory or motor complaints (i.e., early symptoms in the hands). Distal, symmetric polyneuropathies usually have metabolic/

Figure 1 A suggested construct for the approach to neuropathy, using the “what, where, when, and what setting” approach for characterizing polyneuropathy

Only the most common etiologies are found in this figure. Red font indicates predominantly demyelinating polyneuropathies and yellow font indicates predominantly axonal polyneuropathies. CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CMT = Charcot-Marie-Tooth; cryo = cryoglobulinemia; GBS = Guillain-Barré syndrome; hDMN = hereditary distal motor neuropathy (uncommon); HNPP = hereditary neuropathy with liability to pressure palsies; HSN = hereditary sensory neuropathy (uncommon); IgM M protein = also known as distal acquired demyelinating symmetric (DADS) neuropathy or frequently anti-MAG neuropathy; MMN = multifocal motor neuropathy; M protein = monoclonal protein; N-NSS = negative neuropathic sensory symptoms only; P-NSS = positive neuropathic sensory symptoms; SSN = subacute sensory neuropathy (usually associated with malignancy, especially small-cell lung cancer); URTI = upper respiratory tract infection.

Table 1 Important patterns of polyneuropathy with focused differentials (rare causes excluded) and proposed laboratory evaluation

Neuropathy pattern	Common causes	Proposed laboratory studies
Distal symmetric length-dependent neuropathy	Diabetes mellitus	Fasting blood glucose ^a
	B12 deficiency	B12 and methylmalonic acid ^a
	MGUS-associated neuropathy	Serum protein electrophoresis and immunofixation ^a
	Impaired fasting glucose	Oral glucose tolerance test ^a
	Charcot-Marie-Tooth	<i>PMP22</i> duplication, ^a <i>Cx32</i> , ^a <i>PMP22</i> deletion, MPZ, MFN2 ^a
	Uremia	Creatinine, creatinine clearance
	Alcohol	CBC, liver function tests
	Hypothyroidism	TSH
Demyelinating poly(radiculo)neuropathies	Thiamine deficiency	Whole blood thiamine
	CMT1	<i>PMP22</i> duplication, <i>Cx32</i> , MPZ, <i>PMP22</i> deletion
	AIDP	CSF
	CIDP/MADSAM/DADS	Serum protein electrophoresis and immunofixation, CSF
	MMN	GM1 antibodies
Somatic neuropathies with prominent autonomic involvement	HNPP	<i>PMP22</i> deletion
	Diabetes mellitus	Fasting blood sugar
	AIDP	CSF
	Primary systemic amyloidosis	Serum protein electrophoresis and immunofixation
	Sjögren syndrome	ESR, ANA, SS-A, SS-B
	Vincristine toxicity	None
Multifocal neuropathies	Familial amyloidosis	TTR amyloid mass spectrometry
	Systemic and nonsystemic vasculitis	CBC w/diff, CMP, ESR, ANA, CRP, CCP, PR3, MPO, hepatitis B and C serologies, cryoglobulins, HIV, urinalysis
	Entrapment neuropathies	None
	MADSAM	CSF
	HNPP	<i>PMP22</i> deletion testing
Axonal polyradiculo(neuro)pathy	Lyme	Lyme serology and CSF
	Sarcoid	Serum ACE, CSF
	AMAN, AMSAN	CSF
	West Nile	Serum West Nile serology
	Lymphomatous/carcinomatous meningitis	CSF with cytology
Sensory neur(on)opathy	Diabetes mellitus	Fasting blood glucose
	B12 deficiency	B12 and methylmalonic acid
	Sjögren syndrome	ESR, ANA, SS-A, SS-B
	HIV	HIV serology
	DADS	Serum protein electrophoresis and immunofixation
	Paraneoplastic	Paraneoplastic antibodies
	Leprosy	None
Small fiber neuropathy	Diabetes mellitus	Fasting blood glucose
	Impaired glucose tolerance	Oral glucose tolerance test
	Alcohol	CBC, liver function tests
	Sjögren syndrome	ESR, ANA, SS-A, SS-B
	Sarcoidosis	Serum ACE
	Primary systemic amyloidosis	Serum protein electrophoresis and immunofixation
	Familial amyloidosis	TTR amyloid mass spectrometry
	Fabry disease	α -Galactosidase
	HSAN	None

Abbreviations: AIDP = acquired immune demyelinating polyradiculoneuropathy; AMAN = acute motor axonal neuropathy; AMSAN = acute motor and sensory axonal neuropathy; CIDP = chronic immune demyelinating polyradiculoneuropathy; DADS = distal acquired demyelinating symmetric neuropathy; HNPP = hereditary neuropathy with liability to pressure palsies; HSAN = hereditary sensory and autonomic neuropathy; MADSAM = multifocal acquired demyelinating sensory and motor neuropathy; MGUS = monoclonal gammopathy of undetermined significance; MMN = multifocal motor neuropathy; TTR = transthyretin-associated neuropathy.

^a Recommended by American Academy of Neurology practice parameter.¹²

toxic, idiopathic, or inherited etiologies, whereas asymmetric neuropathies are often immune-mediated or infectious.^{1,3,5-7} There are, of course, exceptions, such as the clinical presentation of recurrent, painless, transient mononeuropathies in hereditary neuropathy with liability to pressure palsy. Polyneuropathy associated with immunoglobulin M (IgM) monoclonal protein or anti-MAG autoantibodies is another interesting exception that presents with slowly progressive, distal and symmetric sensory polyneuropathy. Some examples of non-length-dependent, asymmetric (acquired) polyneuropathies are polyradiculopathies (e.g., Lyme neuroborreliosis), polyradiculoneuropathies (e.g., Guillain-Barré syndrome [GBS], chronic inflammatory demyelinating polyradiculoneuropathy [CIP]), dorsal root ganglionopathies (e.g., paraneoplastic subacute sensory neuronopathy, Sjögren-associated sensory ganglionopathy), plexopathies (often immune-mediated), and multiple mononeuropathies (often caused by vasculitis).

When? “When?” refers to the temporal evolution, which can be thought of as including the onset and the progression. We prefer to describe symptom onset based on whether or not the neuropathic symptoms had a convincing date of onset. Most immune-mediated or infectious (e.g., Lyme neuroborreliosis) neuropathies have a definite date of onset. A less-exact date of onset suggests a toxic/metabolic, inherited, or idiopathic etiology. Symptom onset and tempo often correlate because they both represent the pace of disease progression. For example, patients with GBS present with a definite date of onset followed by rapid progression of impairment and disability. Conversely, the symptom onset of an inherited polyneuropathy is usually insidious and followed by very gradual progression.

What setting? “What setting?” refers to the unique clinical circumstance of the patient. This characterization is done by considering the patient’s past medical history, current and past medications, social history, family history, and the review of systems. Knowledge of the risk factors of polyneuropathy and knowledge of symptoms and signs of the risk factors for neuropathy are necessary to take advantage of this information. When constructing the patient’s clinical setting, the clinician must remember to consider first the common causes of polyneuropathy (e.g., diabetes, alcohol, inherited) and search aggressively for any clinical clues that might suggest these etiologies. This is perhaps most important when evaluating a patient for an inherited polyneuropathy, particularly given how common they are. At a minimum, the clinician should ask specifically about each first-degree relative, for example, “Did either parent or any sibling have foot problems similar to yours?” Patients should also be asked at follow-up visits as pa-

Table 2 Some medications that may cause polyneuropathy

Anti-infectious medications
Chloroquine
Dapsone
Isoniazid
Metronidazole
Nitrofurantoin
Dideoxycytidine and other nucleoside analogs
Chemotherapy and anticancer medications
Cisplatin
Taxanes (paclitaxel and docetaxel)
Suramin
Thalidomide
Vincristine
Bortezomib
Antirheumatic and immunosuppressants
Chloroquine
Colchicine
Cardiovascular medications
Amiodarone
Hydralazine
Perhexiline
Propafenone
Psychiatric and sedatives
Disulfiram
Other medications
Pyridoxine (vitamin B6)
Phenytoin

tients often learn important family medical information only after their own diagnosis. Family members should be examined whenever possible. By doing this, clues are often uncovered that would have otherwise never been. Obtaining a precise history of alcohol intake is also very important and, in our experience, often performed perfunctorily by others. It is often illuminating to probe into an alcohol consumption history in a thorough, nonjudgmental, and nonthreatening way.⁸ Past medical and medication history are also important considerations for elaborating the patient’s unique clinical setting. Diabetes, renal disease, malnutrition, HIV, and paraproteinemia are some of the disorders that are risk factors. Toxic polyneuropathy caused by medication is common in the setting of certain chemotherapeutic or anti-HIV treatment exposures (table 2).^{1,9} Age is another important consideration: young patients are much more likely to have a polyneuropathy on a genetic basis, elderly patients are much more likely to have idiopathic polyneuropathy, and middle-age patients are more likely to have acquired polyneuropathy.

The physician must also consider whether the rest of the characterization (i.e., “what?,” “where?,” “when?”

characterization) fits with the clinical setting and also must consider other possible etiologies before implicating an etiology. For example, the comorbidity of diabetes in a patient with polyneuropathy does not necessarily prove diabetes is causative.¹⁰ The examination must also corroborate with the overall characterization. For example, we recently evaluated a 38-year-old man with diabetes complaining of sensory symptoms in the hands and feet whose examination demonstrated not only sensory loss but also pathologically brisk reflexes, prompting a workup that led to the diagnosis of large disk herniation causing a cervical myelopathy.

Electrodiagnostic testing. The fifth step for characterizing a polyneuropathy utilizes EDX testing. EDX can confirm or refute the clinical characterization in terms of “what” and “where” and, to a lesser extent, “when.” EDX can also characterize the polyneuropathy as being primarily axonal or demyelinating. The metabolic/toxic and idiopathic neuropathies usually manifest with prominent axonal injury whereas immune-mediated and inherited neuropathies may be either predominantly axonal or predominantly demyelinating. For example, GBS and CIDP are 2 relatively common demyelinating immune-mediated poly(radiculo) neuropathies. Charcot-Marie-Tooth (CMT) disease 1, the most common group of inherited sensorimotor polyneuropathies, is predominantly demyelinating, whereas CMT2 is predominantly axonal. Nerve conduction studies are particularly helpful here, as patients with CMT1 will have uniform slowing of motor conduction velocities, almost always ≤ 35 m/s in the upper extremities and ≤ 28 m/s in the lower extremities. EDX can also help search for subclinical involvement and provide baseline parameters in case future EDX is necessary to monitor the patient’s course. EDX will be normal in small-fiber polyneuropathy.¹¹

A detailed review of the important causes of polyneuropathy is beyond the scope of this review. Please consult other articles and chapters for information and for additional references about the individual causes of neuropathy. See table 1 for a list of common etiologies and proposed laboratory testing for various patterns of polyneuropathy. See table 2 for a list of some medications that can cause polyneuropathy.

INCORPORATION OF PRACTICE PARAMETERS INTO THE EVALUATION OF DISTAL, SYMMETRIC POLYNEUROPATHY Two practice parameters were published in 2009 that provide recommendations for the evaluation of distal, symmetric polyneuropathy (DSP). These publications were reports of the American Academy of Neurology, American Association

Approach to Polyneuropathy

- Answer “*what, when, where, what setting?*”
- Perform electrodiagnostics
- Use laboratory testing judiciously
- Treat as appropriate

of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation.^{12,13} The parameters were published to provide physicians with evidence-based guidelines for the evaluation of DSP. It is important to remember that these evidence-based guidelines are only about diagnostic testing for the DSP phenotype and, thus, do not supplant the need for a clinical evaluation and EDX characterization of the polyneuropathy. For example, they were not designed to provide diagnostic recommendations that substitute for a careful and comprehensive history, e.g., one that queries patients about alcohol use or family history and other important details of the individual’s history and examination. The authors wrote that the “cause of most polyneuropathies is evident when the information obtained from the medical history, neurologic examination, and EDX studies are combined with simple screening laboratory tests ... Laboratory tests must be interpreted in the context of other clinical information since the etiologic yield of laboratory testing alone is limited by the low specificity of many of the tests.”¹²

The authors of the practice parameters note that most studies suggest that the following laboratory tests are indicated for DSP: complete blood count, erythrocyte sedimentation rate, comprehensive metabolic panel, thyroid function tests, serum B12, and serum protein immunofixation electrophoresis. The evidence is currently most compelling for blood glucose, serum B12, and serum protein immunofixation electrophoresis, of which the test with the highest yield is blood glucose, which comes as no surprise knowing that diabetic polyneuropathy is the most common cause of DSP.

Diabetic polyneuropathy (DPN) symptoms are often predated by silent dysfunction of the nerves with few symptoms, but with progression P-NSS and signs predominate. Onset is fairly gradual and the progression is usually slow.¹⁴ Diabetes mellitus (DM) also appears to be a risk factor for the development of lumbosacral radiculoplexus neuropathy (LRPN), among other less common patterns of neuropathy associated with DM. The presentation of diabetic LRPN (DLRPN) differs dramatically from DPN, with patients experiencing unilateral or asymmetric proximal lower extremity pain and weakness with a definite date of onset. DLRPN is a microvasculitic neuropathy, and is best classified as an immune-mediated radiculoplexus

Figure 2 Decision algorithm for use in cases of suspect hereditary polyneuropathy using family history and electrodiagnostic characterization

*PMP22 denotes peripheral myelin protein 22; MPZ myelin protein zero; PRX periaxin; GDAP1 ganglioside-induced differentiation-associated protein 1; GJB1 gap-junction beta-1 protein (connexin 32); MFN2 mitofusin 2; EGR2 early growth response 2; LITAF lipopolysaccharide-induced tumor necrosis factor α ; RAB7 small guanosine triphosphatase late endosomal protein; GARS glycyl-transfer RNA synthetase; NEFL neurofilament light chain; HSPB1 heat shock protein beta-1.

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neuropathy rather than a metabolic neuropathy.¹⁵ 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).¹⁶ Impaired glucose metabolism has recently been suggested as a cause of chronic idiopathic axonal neuropathy, especially painful, distal, symmetric polyneuropathy. Many specialists suggest that the 2-hour oral GTT is a more sensitive measure of abnormal glucose metabolism compared to fasting plasma glucose or HgA1c. The authors of the practice parameter wrote that "when routine blood glucose testing is not clearly abnormal, other tests for prediabetes (impaired glucose tolerance) such as GTT may be considered in patients with distal symmetric sensory polyneuropathy, especially if accompanied by pain."¹²

Vitamin B12 deficiency is relatively frequently abnormal in patients with DSP. In addition to serum B12 levels, serum methylmalonic acid and homocysteine levels are sensitive indicators of B12 deficiency, with serum methylmalonic acid levels being more specific.¹⁷

Monoclonal gammopathy of undetermined significance (MGUS) is common in the adult population, occurring, for example, in 3% of people over age 50. Monoclonal gammopathies are more common in patients with DSP than in the normal population.¹⁸ Thus, for patients with DSP and a serum monoclonal protein, the clinician must determine whether or not the polyneuropathy is coincidental or secondary to the paraproteinemia. Polyneuropathies associated with paraproteinemias include distal acquired demyelinating symmetric (DADS-M) neuropathy (also known as an ataxic, sensory-

predominant CIDP variant), neuropathy associated with primary systemic amyloidosis, neuropathy of polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome, and neuropathy associated with Waldenström macroglobulinemia. The history and EDX testing are particularly helpful in sorting out whether the paraprotein in a patient with polyneuropathy is coincidental or causal, especially if the physician remembers the following: 1) accompanying systemic symptoms (e.g., fatigue, weight loss) raise concern for primary systemic amyloidosis, POEMS, or malignancy; 2) autonomic symptoms and signs (e.g., orthostatic hypotension) are common in primary systemic amyloidosis; 3) EDX features of primary demyelination are commonly seen in neuropathies of DADS-M and POEMS; 4) the neuropathy is usually axonal when associated with Waldenström macroglobulinemia and primary systemic amyloidosis; and 5) sensory ataxia is a prominent feature of IgM-related polyneuropathies, such as those associated with DADS-M and Waldenström macroglobulinemia. Patients with DADS-M neuropathy also often have serum antibodies to myelin-associated glycoprotein (MAG).¹⁹ Conversely, a coincidental association between the paraprotein (e.g., MGUS) and the polyneuropathy would be more likely in a patient over the age of 50 with a chronic, distal, axonal, symmetric polyneuropathy who lacks prominent ataxia and any systemic or autonomic accompaniments.

DSP is the predominant phenotype in the hereditary polyneuropathies and, consequently, the practice parameter also addresses the role of genetic testing.¹² Pattern of inheritance and electrodiagnostic characterization are 2 particularly important etiologic variables for an inherited polyneuropathy. Most cases of CMT are of the demyelinating form (CMT1). Most cases of CMT1 (e.g., 70%) are caused by duplication of the *PMP22* gene (i.e., CMT1A). Most cases of axonal CMT (CMT2) are caused by mutations of *MFN2*. *Cx32* (*GJB1*) mutations caused the vast majority of X-linked polyneuropathy, which may be predominantly demyelinating or predominantly axonal. The authors recommend that a stepwise evaluation of possible hereditary polyneuropathy be considered in order to improve the efficiency of the evaluation. EDX characterization of suspected hereditary DSP should be performed, followed by an evidence-based, tiered approach (figure 2).¹²

The authors of the practice parameter also recommend that autonomic testing be considered in patients with polyneuropathy and autonomic dysfunction; that nerve biopsy is generally accepted for patients when amyloid neuropathy or vasculitic neu-

ropathy is suspected, and for some atypical forms of CIDP; and that skin biopsy is a validated technique for determining intraepidermal nerve fiber density and may be considered for the diagnosis of DSP, particularly small fiber sensory polyneuropathy.¹³

DISCLOSURE

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The Evaluation of Polyneuropathies

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In the article “The Evaluation of Polyneuropathies” by Burns et al.,¹ the legend for figure 1 should say that the “blue font indicates predominantly axonal polyneuropathies.” The authors regret the error.

Reference

1. Burns TM, Mauermann ML. The evaluation of polyneuropathies. *Neurology*. 2011;76(suppl 2):S6-S13.

Decreased GABA-A Binding on FMZ-PET in Succinic Semialdehyde Dehydrogenase Deficiency

Neurology® 2021;96:1106. doi:10.1212/WNL.0000000000011754

In the article “Decreased GABA-A Binding on FMZ-PET in Succinic Semialdehyde Dehydrogenase Deficiency” by Pearl et al.,¹ the third sentence under the “Anesthetic” subheading in the Methods should read “A bolus dose of 1 mcg/kg was infused....” The authors regret the error.

Reference

1. Pearl PL, Gibson KM, Quezado Z, et al. Decreased GABA-A binding on FMZ-PET in succinic semialdehyde dehydrogenase deficiency. *Neurology*. 2009;73:423-429.

Sex Differences in Treatment and Outcome After Stroke

Pooled Analysis Including 19,000 Participants

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In the article “Sex Differences in Treatment and Outcome After Stroke: Pooled Analysis Including 19,000 Participants” by Carcel et al.,¹ there is an error in table 2. The cells in row “With symptoms (mRS 1–5)” and column “HeadPoST” should read 1,930/4,414 (43.7) for women and 2,393/6,657 (36.0) for men. The authors regret the error.

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