

Laboratory testing in peripheral nerve disorders

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The goal of this review is to guide the physician in ordering laboratory tests for a patient with a neuropathic disorder after the patient has been placed in one of the eleven neuropathic patterns (See this issue: Barohn et al. Pattern Recognition to Neuropathy and Neuronopathy, Pages 4-27, 2023). Once the patient has been placed into one of these eleven patterns, the physician is well on their way to a correct diagnosis for the neuropathic disorder that will ultimately lead to a targeted approach, including treatment. The neuropathic pattern will determine what laboratory tests should be ordered to confirm the diagnosis.

There are many tests one can order in the evaluation of peripheral neuropathy or neuronopathy; however, without using the pattern recognition approach to direct the appropriate laboratory tests the clinician can be left to process multiple laboratory studies that are not relevant to the patient’s problem. We sometimes use the phrase when this occurs: “going down the rabbit hole”. The danger is that you could end up treating a test result and not the relevant diagnosis for that patient.

The most common form of neuropathy that any neurologist or physician sees is the NP2 pattern, symmetric distal sensory loss with or without weakness. These individuals present with distal numbness and tingling in the toes and often burning sensations. Figure 1 lists the blood tests that are reasonable to obtain on a patient with the NP2 pattern. It also lists the tests that should **not** be obtained on a patient with a typical NP2 pattern.

Regarding tests we do not order routinely, we discourage ordering what are often referred to as autoantibody panels. These panels test for antibodies to neural antigens but often combine motor, sensory, and sensorimotor syndromes which may not be relevant to the patient’s clinical phenotype. Rather we suggest only ordering specific antiganglioside antibodies that are appropriate for the clinical pattern in your patient. We will discuss these more later in this review.

Heavy metals do not need to be tested in the blood or urine unless there is a definite history of exposure. Chronic heavy metal exposure does not cause the NP2 pattern of distal sensorimotor neuropathy.

Folate deficiency does not cause peripheral neuropathy; however, it is mistakenly ordered frequently along with B12.

Figure 1

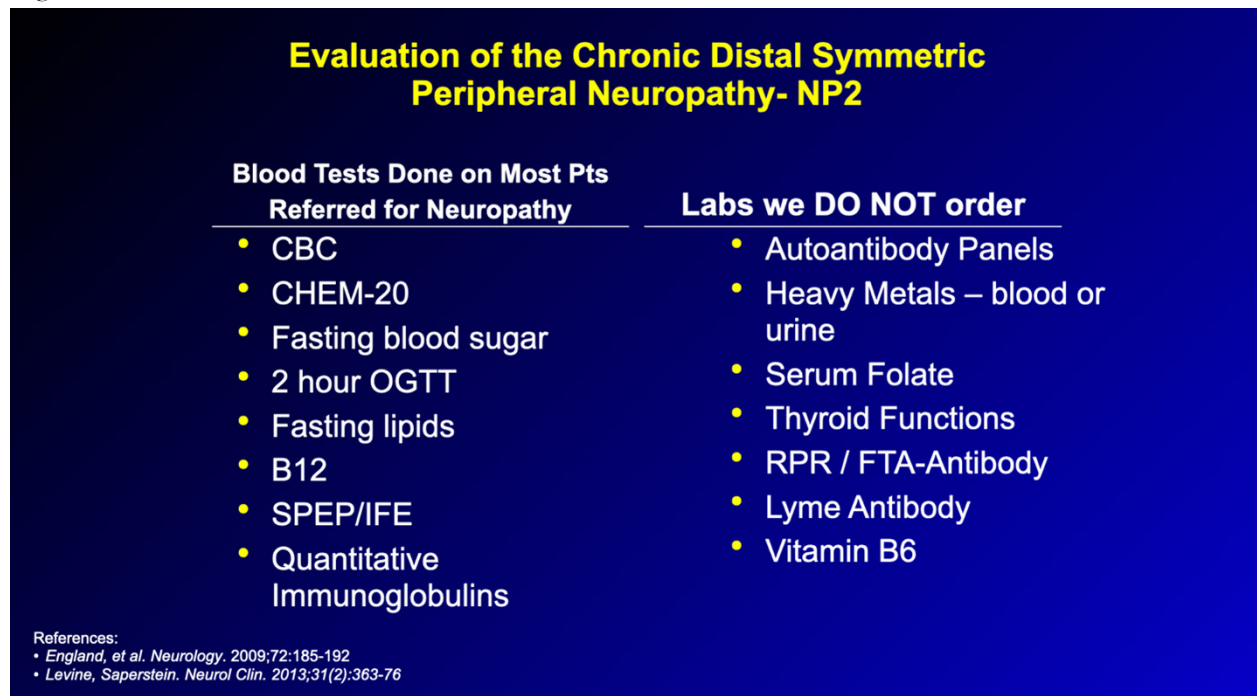


Figure 2

American Diabetic Association Diagnostic Criteria of Diabetes and Prediabetes			
Diagnosis	Hemoglobin A1C	Fasting plasma glucose	2-h oral glucose tolerance test
Normal	<5.7%	<100 mg/dL (5.6 mmol/L)	<140 mg/dL (7.8 mmol/L)
Prediabetes	5.7%-6.4%	100-125 mg/dL (5.6-6.9 mmol/L)	140-199 mg/dL (7.8-11 mmol/L)
Diabetes	≥6.5 %	≥126 mg/dL (7mmol/L)	≥200 mg/dL (11.1 mmol/L)

Definition of the Metabolic Syndrome: Greatest risk factor for type 2 diabetes and cardiovascular disease in the 21st Century (24-42% of US over age 50)

Clustering of metabolic abnormalities:

- Central Obesity
- Insulin resistance
- Hypertriglyceridemia
- Hypercholesterolemia
- Hypertension
- Reduced HDL

References:
• Wang et al, Pediatr Gastroenterol Hepatol Nutr; May 2020; 23(3); 189-230

Syphilis can cause a variety of different peripheral and central nervous system disorders, but it will not present with an NP2 pattern. While there are certainly reports of excessive B6 causing neuropathies, these cases involve extremely high chronic ingestion of B6 supplements, and this information should be acquired by obtaining the history of the patient. Without such a history there is no need to check B6 levels. Thyroid hormone excess or deficiency does not cause peripheral neuropathy. Finally, unless one is in a region in which Lyme disease is common, we do not routinely recommend testing for this disorder.

Regarding the laboratory tests that should be done routinely, it is important to check for diabetes and prediabetes in patients presenting with the NP2 pattern. There are three different measures of glucose metabolism. The hemoglobin A1C is a measure for following someone who has diabetes but not for diagnosing diabetes. Fasting blood glucose, often referred to as fasting blood sugar or FBS is an easy, inexpensive, sensitive, and specific test. The FBS in a healthy person should be less than 100 mm/dL. In a patient with prediabetes, the FBS will be between

100-125 mm/dL. If the FBS is over 125 mm/dL this meets the definition of diabetes mellitus. The two-hour glucose tolerance test is a bit more cumbersome to obtain but it does increase the sensitivity for diagnosing diabetes. (Figure 2)

Therefore, the FBS and the 2-hour glucose tolerance test are both excellent screening tools for diabetes in a patient with the NP2 pattern and are preferable to the hemoglobin A1C.

Metabolic Syndrome is a growing area of interest and is the single biggest risk factor for diabetes or cardiovascular disease (Figure 3). Metabolic syndrome is present in about 1/3 of the population in the United States and consists of a clustering of metabolic abnormalities that include central obesity, insulin resistance, hypertriglyceridemia, hypercholesterolemia, hypertension, and reduced HDL. Figure 3 shows a number of different sets of criteria for the definition of metabolic syndrome. For example, in the Metabolic and Heart Association criteria, three of the following abnormalities would constitute the metabolic syndrome: elevated FBS, treated hypertension, elevated triglycerides, low HDL, or central obesity.

Figure 3

**Commonly used different sets of criteria for diagnosis of metabolic syndrome:
24-42% of the US over age 50**

	WHO (1999)	EGIR (1999)	NCEP ATP III	AHA/NHLBI	IDF
Frame/core criterion	IGT or diabetes and/or insulin resistance plus ≥ 2 other criteria	Insulin resistance (defined as hyperinsulinemia: top 25% of fasting insulin values among the nondiabetics) plus ≥ 2 other criteria	≥ 3 of the 5 criteria below	≥ 3 of the 5 criteria below	Ethnicity specific waist circumference as below or BMI >30 kg/m ² plus ≥ 2 other criteria
Fasting plasma glucose		>110 mg/dL but nondiabetic	> 100 mg/dl	≥ 100 mg/dL or specific treatment for elevated glucose	>100 mg/dL or previously diagnosed T2DM
Blood Pressure	$\geq 140/90$ mmHg	$\geq 140/90$ mmHg or treatment	$\geq 130/85$ mmHg	$\geq 130/85$ mmHg or treatment of previously diagnosed hypertension	$\geq 130/85$ mmHg or treatment of previously diagnosed hypertension
Plasma triglycerides	≥ 1.7 mmol/L (150 mg/dL) or treatment	≥ 2.0 mmol/L (178 mg/dL) or treatment	≥ 1.7 mmol/L (150 mg/dL)	≥ 150 mg/dL (1.7 mmol/L) or specific treatment for hypertriglyceridemia	≥ 1.7 mmol/L (150 mg/dL) or specific treatment for hypertriglyceridemia
HDL- cholesterol	M, <0.9 mmol/L (35 mg/dL); F, <1.0 mmol/L (39 mg/dL)	<1.0 mmol/L (39 mg/dL) or treatment	M, <1.03 mmol/L (40 mg/dL); F, <1.29 mmol/L (50mg/dL)	M, <40 mg/dL (1.03mmol/L); F, <50 mg/dL (1.3mmol/L) or specific treatment for low HDL	M, <1.03 mmol/L (40 mg/dL); F, <1.3 mmol/L (50 mg/dL) or specific treatment for low HDL
Central obesity	M, waist-hip ratio >0.90 ; F, waist-hip ratio >0.85 or BMI >30 kg/m ²	Waist circumference M, ≥ 94 cm; F, ≥ 80 cm	Waist circumference M, >102 cm; F, > 88 cm	Waist circumference M, ≥ 102 cm (40 in.); F, ≥ 88 cm (35 in.)	Waist Circumference: Europids: M, ≥ 94 cm; F ≥ 80 cm; South Asians: M, ≥ 90 cm; F, ≥ 80 cm; Chinese: M, ≥ 90 cm; F, ≥ 80 cm; Japanese: M, ≥ 85 cm; F ≥ 90 cm

Figure 4

Evaluation of Metabolic Syndrome, Prediabetes, and Diabetes

- History and neurologic exam should be conducted along with evidence-based laboratory tests for both diabetes and prediabetes
 - Fasting glucose or 2 hour OGTT
 - Hgb A1c is not considered a sensitive test for screening
 - Blood pressure & BMI should be recorded
 - Evaluation of lipid profile
 - History of diet, exercise or level of sedentary behavior
- A clear pattern is seen linking MetS to CSPN
 - Obesity, prediabetes and diabetes, dyslipidemia all are associated with elevated risk of CSPN
 - MetS seen to increase risk of neuropathy in type 1 & 2 DM

References:
 • Kazamel, Stino, Smith. Muscle and Nerve; March 2021. 63(3) 285-293

Therefore, it is important to take into account all of these parameters when evaluating a patient for the NP2 pattern of neuropathy (Figure 4). There is a clear association between the metabolic syndrome and diabetic distal sensory polyneuropathy (DSPN) and cryptogenic sensory polyneuropathy (CSPN) or the NP2 pattern of peripheral neuropathy. We also know that in a patient who has

diabetes, type 1 or type 2, if they have metabolic syndrome in addition to their diabetes their risk of neuropathy goes up significantly. Therefore, metabolic syndrome does seem to be an independent risk factor even separate from glucose that links the metabolic syndrome to the NP2 pattern of neuropathy.

Figure 5

Evaluation of Metabolic Syndrome, Prediabetes, and Diabetes

- MetS neuropathy and early DPN are associated with preferential injury to small nerve fibers
 - Epidermal fibers are capable of regeneration and sprouting despite being disproportionately prone to metabolic, vascular, and mechanical injury
 - Small unmyelinated axons are prone to injury from obesity and hypertriglyceridemia
 - Large myelinated fibers are susceptible to injury from hyperglycemia
- Autonomic neuropathy is also observed manifesting as cardiac vagal, cardiac adrenergic, vasomotor, gastrointestinal, genitourinary, and secretomotor dysfunction
- The timing of autonomic neuropathy relative to the onset of SFN in MetS is unknown but cardiac vagal autonomic dysfunction occurs early in the disease because obesity leads to a reduction in heart rate variability
- Diagnosis of DPN is determined by abnormality in either nerve conduction studies(NCS) or measure of small fiber function such as skin biopsy for IENFD
 - NCS cannot be used solely to diagnose MetS-related Neuropathy
 - Skin punch biopsy evaluation for IENFD is the “gold standard” for SFN diagnosis

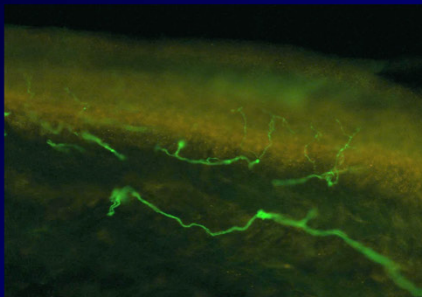
References:
 • Kazamel, Stino, Smith. Muscle and Nerve; March 2021. 63(3) 285-293

Figure 6

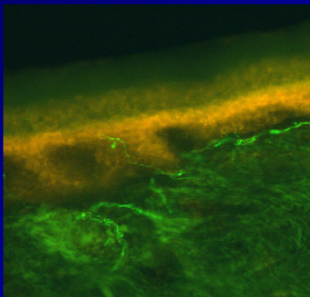
Small Fiber Neuropathy

- Symptoms may be distal, proximal, or multifocal
- Symptoms may be persistent or intermittent
- In Isolated SFN- Exam and NCVs are normal
- Some patients can have non-length dependent symptoms
- Reported sensitivity and specificity of skin biopsy is 88% and 92%
- But useful for the diagnosis of CSPN (NP2) when large fiber signs are absent on exam and NCVs are normal.

Normal



Abnormal



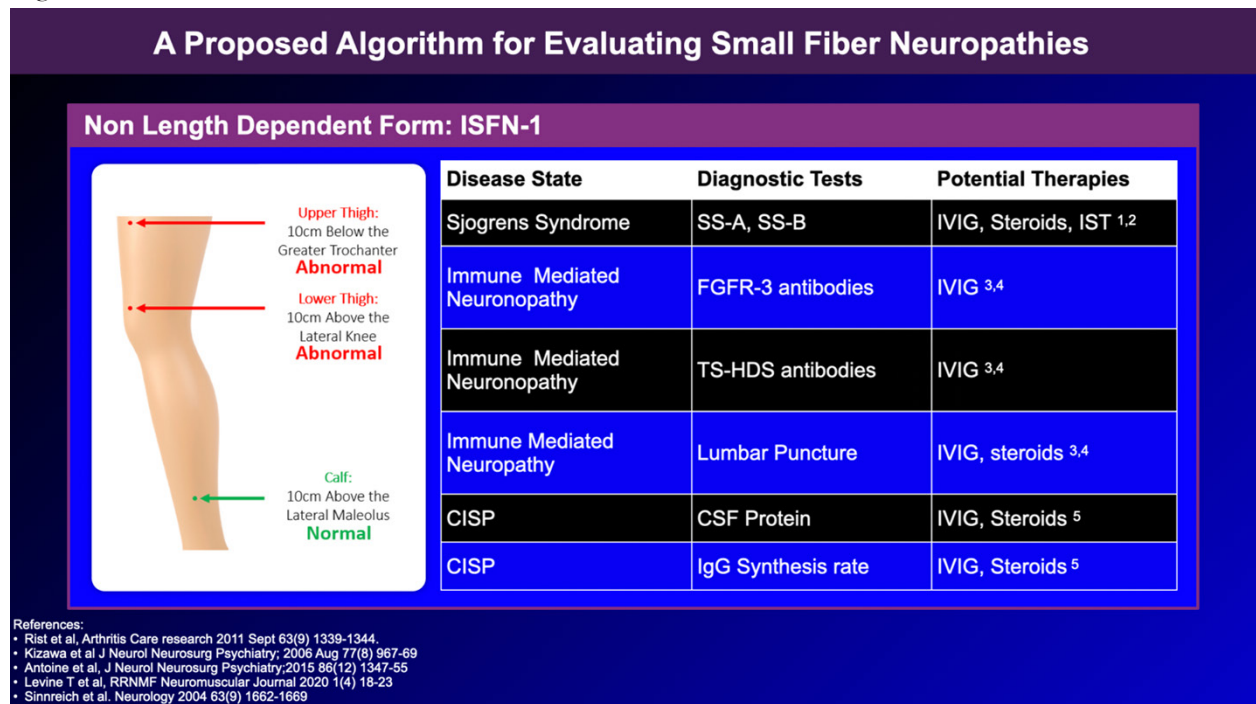
Metabolic syndrome in the early phases of diabetic neuropathy tends to affect the smallest nerves first (Figure 5).

These small nerves, the epidermal sensory nerve fibers, seem to be very susceptible to injury from obesity and hypertriglyceridemia. The large, myelinated fibers seem to be more susceptible to damage from hyperglycemia. Autonomic symptoms and signs can be associated with

small fiber involvement. Nerve conduction studies alone may not be able to diagnose the neuropathy associated with metabolic syndrome. Nerve conduction studies measure large fiber physiology and cannot detect neuropathy when only small nerve fibers are involved. Rather, skin punch biopsies assessing small intradermal nerve fibers is probably a more sensitive test to look for nerve damage (Figure 6).

What do we mean when we talk about intraepidermal

Figure 7



nerve fiber densities? Figure 6 shows two skin punch biopsies. The area at the top is the epidermal layer. Just beneath that is the basement membrane and the melanocytic layer and below that is the dermis. The figure on the left shows normal intraepidermal nerve fiber density and the figure on the right shows decreased intraepidermal nerve fiber density.

In skin biopsies for intraepidermal nerve fiber density, the nerves come in parallel to the surface of the skin and then they branch upwards. These small unmyelinated nerve fibers are the nerve fibers that provide sensation throughout our body. When these small nerve fibers are damaged, this typically results in distal sensory loss or abnormal sensory sensations. Therefore, the pattern is the distal NP2 in most cases. Rarely some small fiber neuropathies can have proximal or multifocal patches of sensory involvement. When only small fibers are involved, vibration and proprioception, and reflexes on the neurologic exam are normal and nerve conduction studies are normal. In these cases, a skin biopsy can be helpful in documenting and quantifying small fiber sensory loss. If the patient presents with distal sensory loss and/or neuropathic pain distally, and either proprioception or vibration, or reflexes are abnormal then you know that both large and small fibers are involved, and the nerve conduction studies are likely to be abnormal. In these cases, a skin biopsy is probably not going to be useful as you have already documented a neuropathy. In other words, if the nerve conduction studies are abnormal you will not learn anything additional from the

skin biopsy. The skin biopsy is most useful as a tool in cases where a patient has sensory symptoms and a normal exam and normal nerve conduction studies. In these cases, the skin biopsy has a sensitivity and specificity of about 90%. We recommend that skin biopsies are taken from three sites: one from just above the ankle, one from just above the knee, and one from below the hip. The reason for doing this is to demonstrate objectively the pattern of small fiber loss.

Based on the patient's symptoms, signs, and skin biopsy, there are four different intraepidermal small fiber neuropathy presentations- IFSN-1; IFSN-2; IFSN-3; IFSN-4. If you have a patient with upper thigh skin biopsies that are abnormal, but lower thigh and calf biopsies are normal, this is referred to as the ISFN-1 presentation (Figure 7) This is a non-length-dependent small fiber neuropathy which has been shown to predict an autoimmune etiology.

The length-dependent distal pattern, where the skin punch biopsy is abnormal at the lower thigh and calf and normal at the upper thigh is the IFSN-2 presentation of small fiber neuropathy. This falls in the spectrum of the clinical NP2 pattern and most often due to diabetes (DSPN), cryptogenic (CSPN), or chemotherapy-induced neuropathy (CIN). (Figure 8)

There is an entity called Wartenberg's sensory neuritis which is a patchy distribution of sensory loss and pain both proximally and distally. In other words, there is multifocal patchy sensory loss and pain. For example, the calf and upper thighs may be involved clinically but the lower thigh is normal, and this can be at times documented or supported

Figure 8

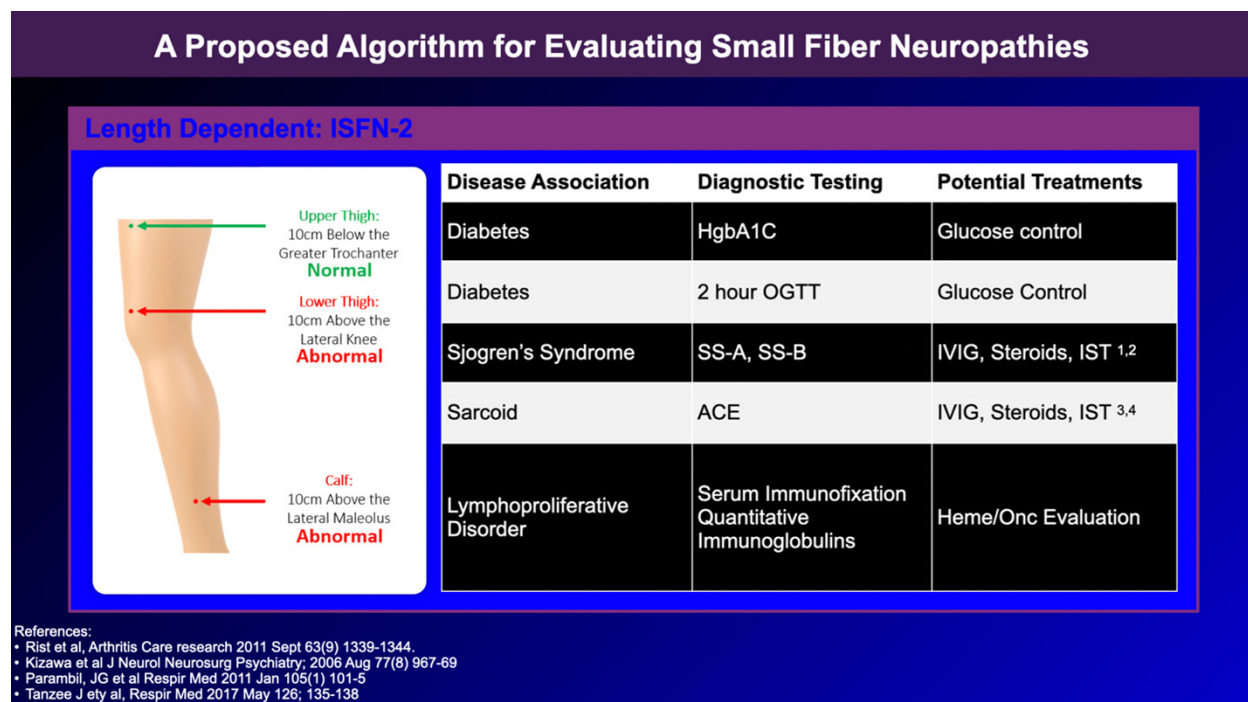
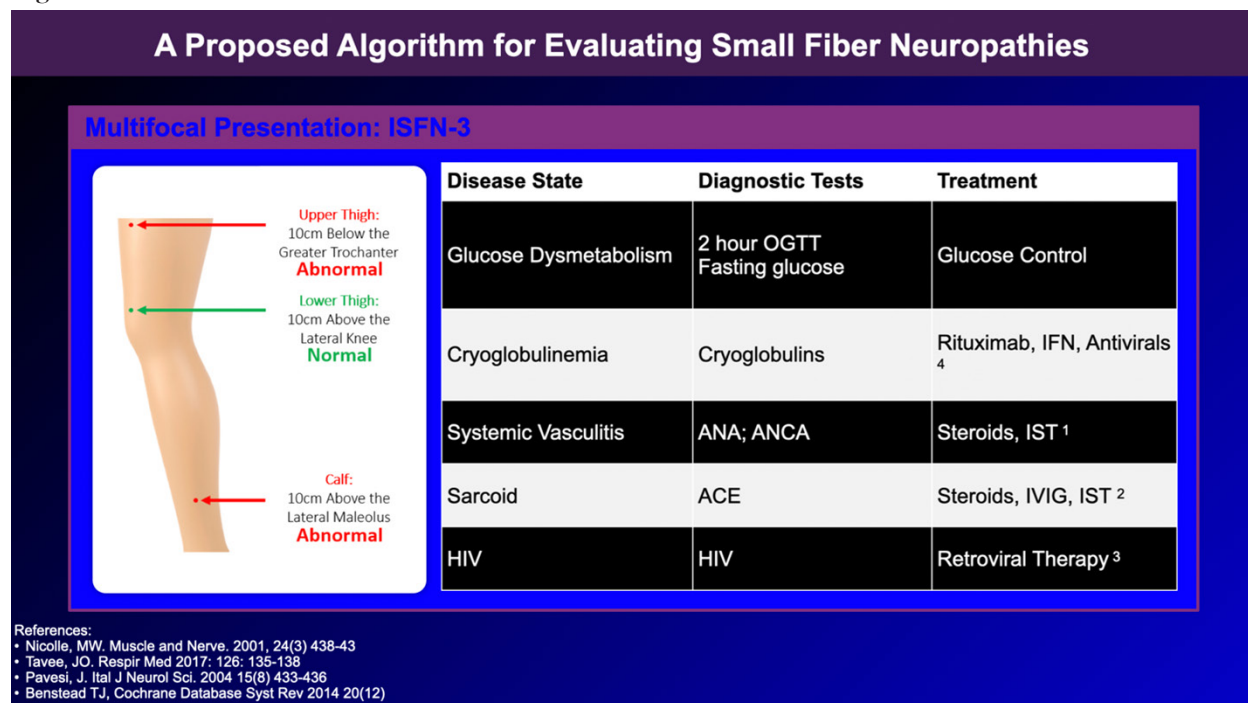


Figure 9



by skin biopsies showing a similar distribution of small fiber sensory loss. We have referred to this as the ISFN-3 presentation. (Figure 9)

There are some pure autonomic neuropathies in which the intraepidermal nerve fiber density is normal

but the nerve fiber density in the sweat glands in the skin are reduced. This has been referred to as the ISFN-4 presentation. (Figure 10)

Regarding B12 deficiency, serum B12 is often a poor measure of B12 deficiency. In B12 deficiency, methylmalonic

Figure 10

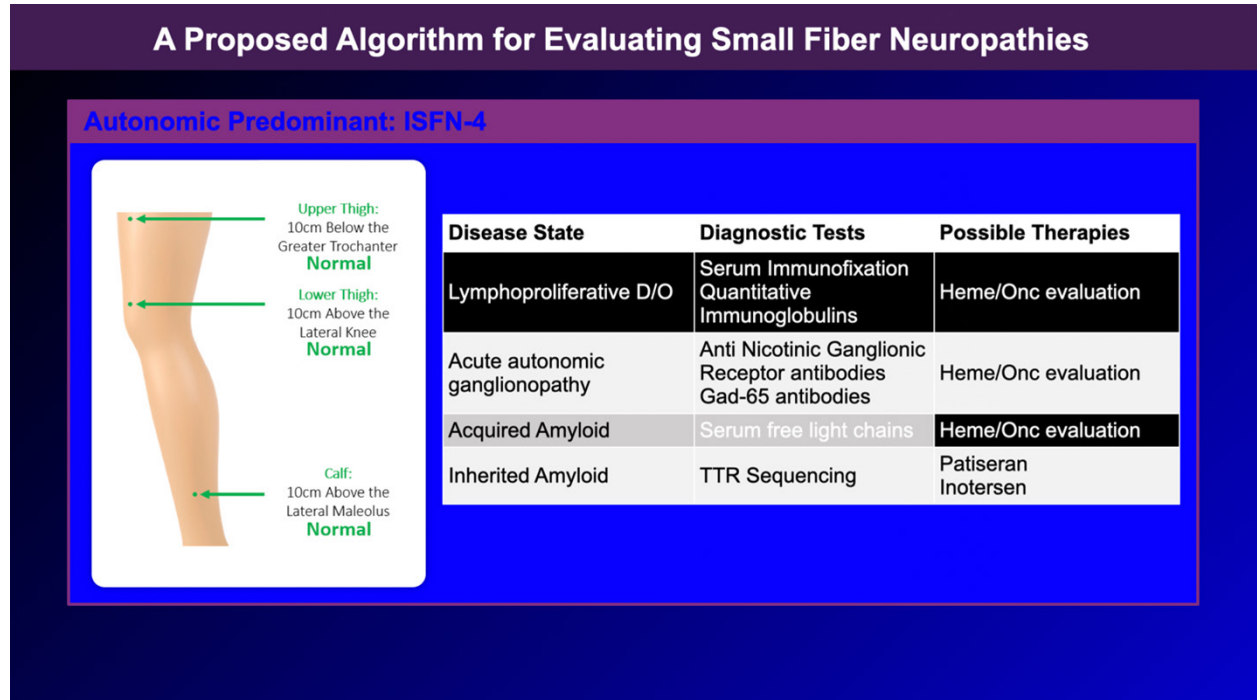
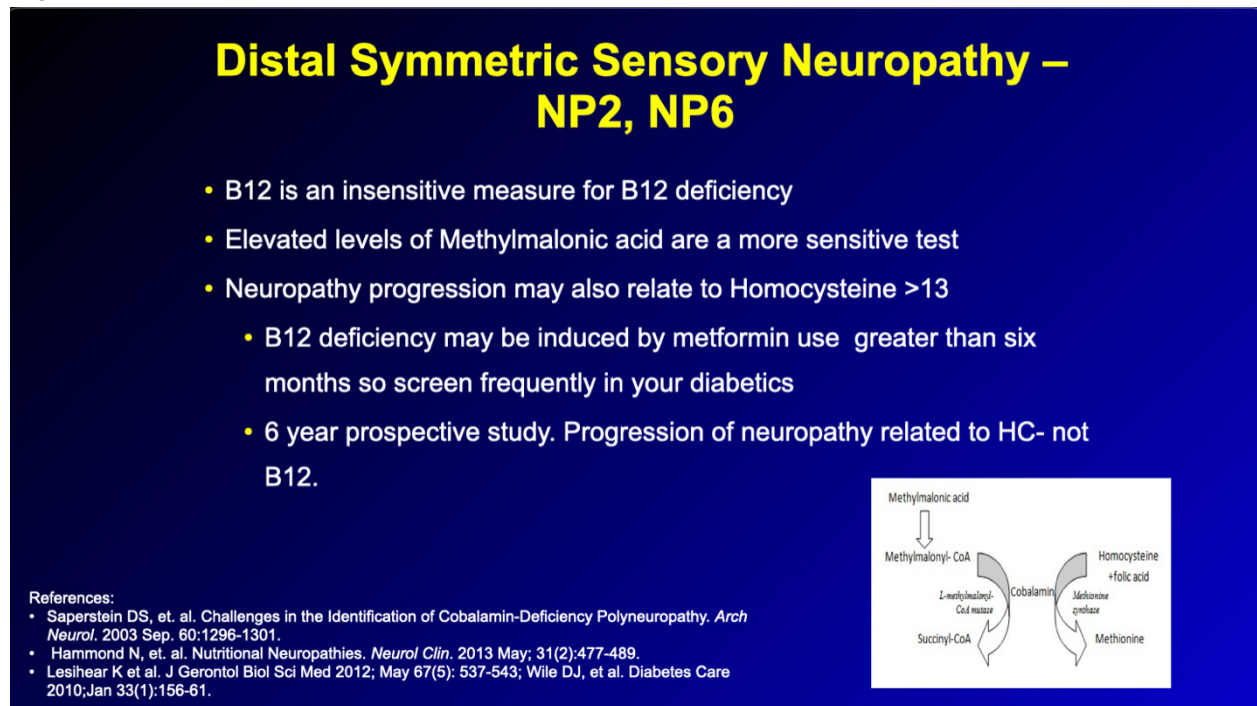


Figure 11



acid builds up and is toxic to nerves. Therefore, in evaluating for possible B12 deficiency it is recommended to do a serum B12 level with a serum methylmalonic acid level. Blood methylmalonic levels are elevated in B12 deficiency. Blood homocysteine levels can also be elevated. Homocysteine is probably not a direct cause of neuropathy. However, when homocysteine is elevated, it does predict a faster progression of the neuropathy. Elevated homocysteine may be a measure of metabolic syndrome, and it may

be that it is the metabolic syndrome that is causing the progression of their neuropathy. For diabetic patients who are on metformin, it should be recognized that this drug can induce a B12 deficiency. Therefore, we recommend that diabetics on metformin have B12, methylmalonic acid, and homocysteine levels checked if they have a worsening neuropathy to make sure there is not a second cause due to the metformin.

Figure 12

Chronic Distal Symmetric Sensory Neuropathy – NP2

- **Paraproteins**
 - SPEP
 - Serum immunofixation
 - Quantitative Immunoglobulin
 - Serum free light chains
 - How and when to send to Heme/Onc.
 - Evaluate for lymphoma, Waldenstrom's Myeloma

Figure 13

MGUS Risk Stratification

- Risk-stratification model that is useful in predicting the risk of progression of MGUS to a malignancy
 - Serum monoclonal protein level ≥ 1.5 g/dL
 - Non-IgG MGUS
 - Abnormal serum free light chain ratio (i.e., ratio of kappa to lambda free light chains < 0.26 or > 1.65)
- The absolute risk of disease progression over 20 years for patients with:
 - 3 of the above risk factors (high-risk MGUS) — 58%
 - 2 risk factors (high-intermediate risk MGUS) — 37%
 - 1 risk factor (low-intermediate risk MGUS) — 21%
 - No risk factors (low-risk MGUS) — ~5%

References:

- Rajkumar et al. Mayo Clin Proceed. 2010 85:10 945-948.

Regarding testing for a paraprotein in the setting of a neuropathy, it is recommended that patients have a serum protein electrophoresis (SPEP) blood test or quantitative immunoglobulins to evaluate the total of the antibody classes. In addition, we recommend a serum immunofixation to look for small spikes of abnormal proteins. If any of these are abnormal an additional test for serum-free light chains and urine for light chains should be obtained as an evaluation for underlying blood-based dyscrasias. All of

the tests for serum paraproteins are designed to search for an underlying lymphoproliferative disorder. However, not all patients with a serum paraprotein have an identifiable lymphoproliferative disorder and in these cases, we classify the abnormality as a monoclonal gammopathy of unknown significance (MGUS). The incidence of paraproteins increases with age. Over the age of 75, up to 5% of the population may have a MGUS. If a paraprotein is found (also often called monoclonal protein) attention needs to

Figure 14

Chronic Distal Symmetric Sensory Neuropathy		
Potential Etiology	Tests to Order	Pattern
Diabetes Mellitus	Fasting glucose, HgbA1c	NP2, NP4
Impaired Glucose Tolerance	2 hour glucose tolerance test	NP2, NP4
Metabolic Syndrome	Fasting glucose, Lipids, BMI,	NP2
B12 deficiency	B12 levels; methylmalonic acid; Homocysteine	NP2, NP6
Paraproteinemia	Quantitative Immunoglobulins Serum Immunofixation Serum Free light chains	NP2, NP1
Small Fiber Neuropathy	Skin biopsy if NCS normal	NP1, NP2, NP3

Figure 15

Acute/Subacute Asymmetric Sensory Neuronopathies – NP9
<ul style="list-style-type: none"> • Predominantly large fiber posterior column involvement with ataxia and dysmetria as main complaints <ul style="list-style-type: none"> – Pseudoathetosis found in many cases • These may be non-length dependent because of effects on cell body rather than nerve process • Diagnosis often on the NCS: <ul style="list-style-type: none"> • Diffusely absent sensory responses with relative preservation of motor responses • Higher likelihood for an autoimmune mediated process with neuronopathies than with neuropathies

be focused on three aspects: the amount of the monoclonal protein, the type of monoclonal protein, and whether there are any free light chains.

If we look at the stratification in approaching a patient with a MUGS outlined in Figure 13, there are three risk factors that we identify. The type of Ig (IgM, IgG), the amount of the protein, and the ratio of kappa to lambda light chains. If the patient has an IgG level below 1.5gm/dl and a normal light chain ratio, the chance of any malignancy

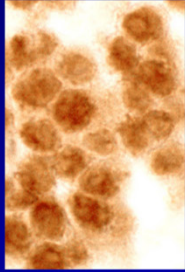
is very low. On the other hand, a patient with 3 gm/dL of paraprotein that is IgM and an abnormal free light chain ratio, has a very high likelihood of malignancy and needs a referral to hematology.

Figure 14 summarizes the information we have reviewed up to this point regarding diabetes, metabolic syndrome, B12 deficiency, paraproteins, small fiber neuropathy, and the pattern most often associated with these abnormalities.

Figure 16

Sensory Neuropathies – NP9

- Paraneoplastic – Anti Hu Antibodies
 - 50% with no known malignancy at presentation
 - Small cell lung cancer most common
 - Prostate, breast, ovary less common
 - 75% of patients with no motor involvement
 - Progresses over days to weeks
 - There are often other associated syndromes
 - Autonomic in as much as 30%
 - Limbic encephalitis with or without seizures
 - CSF usually has pleocytosis and elevated protein



Staining of neuronal nuclei
Courtesy Alan Pestronk, MD

Figure 17

Sensory Neuropathies – NP9

- Described in Fibroblast growth factor-3 (FGFR-3) and trisulfated disaccharide IdoA2S- GlcNS-6S (TS-HDS) Syndromes ¹
- Sjogren's syndrome
 - The neuropathy often has associated features
 - Typically slowly progressive, but can be acute
 - Adie's pupil in as many as 25%
 - Constipation or bladder involvement
 - If found with cyroglobulins predicts a worse prognosis

References:
• Pestronk et al, Muscle and nerve 2012, Antoine et al, Neurology 2013.

The NP9 pattern often indicates a neuropathy where the damage is to the sensory cell body (Figure 15). NP9 affects large sensory fibers and can lead to ataxia, dysmetria, and very often astereognosis. This can be non-length dependent and asymmetric. Nerve conduction studies show that sensory responses are absent and motor responses are normal. These disorders are most likely to be

autoimmune.

Often there is an underlying malignancy as in the presence of anti-Hu antibodies. (Figure 16)

However, occasionally a malignancy is not found (Figure 17). In these instances, some cases have been associated with autoantibodies to FGFR-3 and TS-HDS. Other cases are associated with Sjogren's syndrome and

Figure 18

Vitamin E Deficiency- NP9

- Causes
 - A Beta Lipoproteinemia
 - Vitamin E Transporter deficiency
 - Malabsorption
 - Whipple's disease
 - Cystic Fibrosis
 - Chronic Pancreatitis
 - Neuropathy
 - Large fiber modalities with a sensory ataxia
 - Pseudoathetosis when severe
 - Often with up going toes
 - Can have associated ophthalmoplegia

References:
 • Jackson CE, Amato AA, Barohn RJ. *Muscle Nerve* 1996;19(9):1161-5

Figure 19

CANVAS: Cerebellar Ataxia with Neuropathy and Vestibular Areflexia Syndrome

- Genetic: AAGGG repeat expansion in RFC1 gene
- Recessive, dominant, but most sporadic
- Neuropathy is a sensory neuronopathy
 - Severe proprioception loss
- Onset sixth decade
- Dry cough and autosomal dysfunction

References:
 • Cortese, A., et al. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome due to RFC1 repeat expansion. *Brain* 2020; 143(2): 480-490.
 • Cortese, A., et al. Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS): genetic and clinical aspects. *Practical Neurology* 2022; 22: 14-18.
 • Ronco, R., et al. Truncating Variants in RFC1 in Cerebellar Ataxia, Neuropathy, and Vestibular Areflexia Syndrome. *Neurology* 2023; 100: e543-554.
 • Gisatulin, M., et al. Clinical spectrum of the pentanucleotide repeat expansion in the RFC1 gene in ataxia syndromes. *Neurology* 2020; 95: e2912-2923.

may have SS-A or SS-B serum positivity. Clinically some of these Sjogren's patients with neuronopathy can also have Adie's pupil, severe constipation, and bladder involvement suggesting autonomic issues.

Vitamin E deficiency can also present with an NP9 pattern (Figure 18). Vitamin E deficiency is generally only seen in patients with a severe malabsorption issue or if they have a specific deficiency like abetalipoproteinemia

or vitamin E transporter deficiency. In many vitamin E deficiency patients, there are also central nervous system findings including upgoing toes and ophthalmoplegia.

Recently, a genetic syndrome has been described consisting of cerebellar ataxia, neuropathy, and vestibular dysfunction called CANVAS. The neuropathy is believed to be a sensory neuronopathy with profound proprioceptive sensory loss. Many patients have a chronic cough, and

Figure 20

Acute/Subacute Asymmetric Sensory Neuronopathies		
Potential Etiology	Tests to Order	Pattern
Sjogren's syndrome	SS-A, SS-B	NP2, NP9, NP10
HIV	HIV serology	NP1, NP2, NP3, NP9
Paraneoplastic	Hu serology	NP9
Vitamin E deficiency	Vitamin E levels	NP2, NP9
Tabes Dorsalis	RPR	NP2, NP9
Vitamin B6 toxicity	B6 levels	NP9
Immune Mediated	TS-HDS FGFR-3 Antibodies	NP9
CANVAS	AAGGG expansion on RFC1 gene (Southern Blot)	NP9

Figure 21

Pure Motor Patterns Without Upper Motor Neuron Signs	
<ul style="list-style-type: none"> • Kennedy's Disease (NP8) • Multifocal Motor Neuropathy (NP5) <ul style="list-style-type: none"> • Slowly progressive weakness: upper > lower extremity <ul style="list-style-type: none"> • Atrophy typically present when they come to attention • Wrist extensor and finger extensor weakness • IgM antibodies against GM-1- approximately 50% • Motor conduction block- may be as low as 50%-70% • Acute motor axonal polyneuropathies <ul style="list-style-type: none"> • Post infectious related to campylobacter jejuni • Patients develop IgG antibodies to GM-1 • Should analyze CSF to rule out autoimmune, infectious or malignant causes • Avoid ganglioside antibody panels <ul style="list-style-type: none"> • Wolfe et al. Muscle Nerve 1997;20(10):1275-1283 	

some have autonomic dysfunction the genetic defect is a novel biallelic AAGGG expansion in the replication factor subunit 1 complex (RFC1). The repeat expansion cannot be detected on currently available next-generation sequencing panels and requires identification by time-consuming southern blotting. This condition is now thought to be one of the most common causes of late-onset genetically mediated

cerebellar ataxia. A patient with a combination of cerebellar ataxia and sensory neuropathy may have this disorder.

Figure 20 summarizes the information about sensory neuropathy discussed above. It also mentions that rarely HIV, Tabes Dorsalis, and vitamin B6 toxicity can have an NP9 presentation.

Figure 22

Pure Motor Neuropathies		
Potential Etiology	Tests to Order	Pattern
Acute Motor Axonal Neuropathy	CSF GM-1 antibodies	NP1, NP7
Multifocal Motor Neuropathy	GM-1 Antibodies Serum Immunofixation Quantitative Immunoglobulins Serum free light chains	NP5
ALS- Hyperreflexia	EMG/NCV Imaging	NP5
Kennedy's disease	Androgen receptor gene	NP8
West Nile Virus	CSF for WNV PCR	NP5
Enterovirus-68	CSF viral culture/PCR	NP5
SMA	SMA gene	NP7

Pure motor patterns are often some of the most difficult cases mainly due to the fact that if a patient comes in with pure motor weakness as a result of neuropathic disorder, it is more likely to be due to amyotrophic lateral sclerosis- NP5 (Figure 21). If upper motor neuron signs are present ALS is definitely the most likely diagnosis. On the other hand, if upper motor neuron signs are not present the diagnosis may be a pure lower motor neuron disease often referred to as progressive musculature atrophy (PMA). However, there are other causes that can produce pure motor patterns without upper motor neuron signs. Kennedy's disease also known as X-linked spinobulbar atrophy is a genetic disorder affecting men and in addition to limb involvement has tongue, face, and pharyngeal motor weakness (NP8). It is usually symmetric and proximal more than distal weakness in the extremities. The diagnostic test is a genetic assay showing an excess number of triplet repeats in the SMA gene on the X chromosome.

Multifocal motor neuropathy (NP5), like ALS, can present with distal unilateral hand weakness but without upper motor neuron signs and the weakness may be confined at an early stage to one or two nerves. MMN has a predilection for radial nerves, so wrist and finger drop are prominent. It is important to recognize as it is treatable. Half of these patients have serum GM1 antibodies in the

serum. Conduction block may only be seen in 50-70% of patients, so a clinical diagnosis is critical in these cases.

Some acute motor neuropathy syndromes are acute and symmetric and mimic the Guillain-Barré syndrome but without sensory symptoms, signs, or objective sensory abnormalities on nerve conduction studies or nerve biopsy. These GBS variants are usually axonal polyneuropathies and not demyelinating. The usual term for these disorders is acute motor axonal neuropathy (AMAN). AMAN usually follows a gastrointestinal infection with *Campylobacter jejuni* and has IgG antibodies to GM-1. AMAN cases are treated like typical GBS but often have a poor prognosis.

Autosomal recessive spinal muscular atrophy presents with the NP7 pattern with symmetric proximal and distal weakness and can present from infancy to young adulthood. The diagnosis is based on genetic testing for SMN-1 gene deletions and also determining the number of copies of SMN-2. Now that we have therapies for SMA it is important to consider this diagnosis even in the non-pediatric population.

West Nile virus can present as a polio-like syndrome at any age. Enterovirus can produce a paralytic polio-like syndrome in infancy and childhood.

Figure 22 summarizes the entities discussed above, and the associated patterns and laboratory tests.

Figure 23

Acute Mixed Motor Sensory Neuropathies

- **GBS – NP1**
 - More common after upper respiratory infection
 - Examination of CSF for albuminocytologic dissociation
 - Autoantibodies can be found in 30-50%
 - IgM GAINAc-GD1a
 - IgM to Tubulin
 - IgM to Heparan Sulfate
- **AMSAN – NP1**
 - More common after campylobacter infection
 - Examination of CSF for albuminocytologic dissociation
 - Autoantibodies can be found in 30-50%
 - IgM to GM-1
 - IgM to GM1b
 - IgM to GalNac-Gd1a

References:
• Pestronk A, et al; Journal of Neuroimmunology; 91(1): 204-209

Figure 24

Acute Mixed Motor Sensory Neuropathies

Potential Etiology	Tests to Order	Pattern
GBS	CSF	NP1
AMSAN	CSF	NP1
Mononeuritis Multiplex	ESR, ANA, ANCA, RF, SS-A/B Hepatitis B and C serologies cryoglobulins HIV ACE Nerve biopsy	NP3

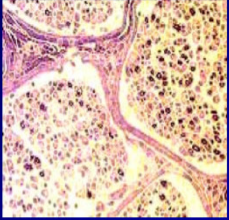
Guillain-Barre syndrome, while often appearing predominantly motor usually has sensory symptoms and signs and often can have sensory nerve conduction study abnormalities (Figure 23, 24). Occasionally IgG and IgM antibodies to a number of nerve glycoproteins have been identified. The pure axonal form of motor and sensory

Guillain-Barré is often referred to as acute motor sensory and motor sensory axonopathy (AMSAN), and like AMAN has a poorer prognosis than GBS. GBS, AMSAN, and AMAN all typically have elevated CSF protein without an elevated cell count, or the so-called albumin-cytologic dissociation.

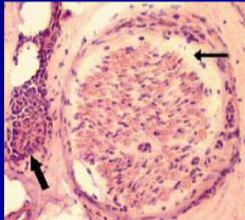
Figure 25

Acute Mixed Motor Sensory Neuropathies

- Mononeuritis multiplex – NP3
 - Best indication for nerve biopsy
 - Multifocal, Asymmetric-
 - Asymmetric neuropathies are more likely to be treatable
 - Typically this represents a vasculitis which can be associated with underlying diseases
 - Cryoglobulins
 - Hepatitis
 - Systemic Vasculitis
 - HIV
 - Sarcoid



Differential Fascicular Loss



Inflammation
Perineural Edema

Why have nerve biopsies decreased? Only rarely are nerve biopsies now needed as a supportive laboratory test for the diagnosis of neuropathy. This is usually performed in cases of possible vasculitic neuropathy that presents with the NP3 pattern (Figure 25). However, other than in vasculitis nerve biopsies are rarely performed in the modern era. Why? We have gained a better understanding of clinical phenotypes and we have gotten better at interpreting nerve

conduction studies; we use more genetics, imaging, and spinal fluid than we did previously. If you make a provisional diagnosis using pattern recognition and tests short of a nerve biopsy, and the patient continues to deteriorate despite therapies, this may be an indication of the need for a nerve biopsy. On the other hand, if the patient has an acute presentation with pain as part of the NP3 pattern, you might consider treating the patient with prednisone.

Figure 26

Subacute Mixed Motor and Sensory Neuropathies

- Progressive symptoms for greater than 4 weeks but less than 8 weeks
- Helpful to distinguish axonal from demyelinating disease process
- NCVs are often mixed axonal and demyelinating
- If diseases are progressive consider CSF and nerve biopsy
- Demyelinating
 - SIDP, MADSAM, MAG, DADS, HNPP
 - Use the patterns to distinguish
- Axonal
 - Lyme, Sarcoid, WNV, Malignancy, Vasculitis

Figure 27

Subacute Mixed Motor and Sensory Neuropathies

Potential Etiology	Tests to Order	Pattern
SIDP	CSF	NP1
MADSAM	CSF	NP3
DADS	CSF Serum immunofixation, quantitative immunoglobulins, serum free light chains MAG titers	NP2
MAG/Nodopathies	MAG titers Neurofascin Contactin	NP2
HNPP	PMP 22 deletion	NP3
Lyme	Lyme serology and CSF	NP1, NP2, NP3
Sarcoid	ACE, CSF	NP2, NP3
West Nile virus	West Nile serologies and CSF	NP5
Lymphomatous/Carcinomatous meningitis	CSF with cytology	NP4
If tests are normal and marked Progressive weakness	Nerve biopsy	

Acute neuropathies are defined as disorders with a duration under four weeks. Chronic neuropathy has a duration of over eight weeks with progression. Neuropathic disorders with progression between four and eight weeks are considered subacute. Subacute immune demyelinating polyneuropathy or SIDP falls into this category, between GBS and CIDP (Figure 26, 27). These cases remain difficult

to approach. The dilemma is often: Should one treat them as Guillain-Barré only for a limited time or as CIDP on a chronic basis?

Nerve conduction studies can be helpful in subacute mixed motor and sensory neuropathies. Progressive weakness that is subacute or chronic that is associated with demyelinating electrophysiologic abnormalities

Figure 28

Laboratory Evaluation of Subacute Mixed Demyelinating Neuropathies

- Multifocal Acquired Demyelinating Sensory and Motor neuropathy (MADSAM) (NP3)
 - Asymmetric, Distal, Upper Limb Predominant Demyelinating
 - CSF protein elevated
 - No specific autoantibodies
- Distal Acquired Demyelinating Symmetric neuropathy (DADS) (NP2)
 - Distal, Demyelinating— i.e. prolonged distal latencies
 - With or without MAG antibodies
 - CSF protein elevated
- Nodopathies (NP-2)
 - Neurofascin
 - Contactin
 - Contactin associated protein 1
- Hereditary Neuropathy with Pressure Palsy (HNPP) (NP3)
 - Deletion of PMP 22 gene
 - Asymmetric, Focal, Motor Sensory
 - Often with evidence for multiple compressive neuropathies

superimposed on axonal changes should prompt aggressive therapy with immunomodulating agents.

There are a series of disorders called nodopathies (NP-2) (Figure 28). In nodopathies, there is an antibody-mediated attack on the nodes of Ranvier, so it is not directly demyelinating but it is interfering with conduction. In those patients, their exam and nerve conduction studies may look like a CIDP-type patient, but these patients are difficult to treat and do not respond to IVIG and steroids. The antibody

in these cases is an IgG 4 and may respond much better to rituximab than they do IVIG or steroids. Therefore, if a patient does not respond to IVIG with a subacute or chronic inflammatory demyelinating polyneuropathy consider searching for antibodies associated with the nodopathies. Hereditary neuropathy with pressure palsy (HNPP) can also present with a mononeuritis multiplex NP5 pattern. The supporting laboratory test is a genetic test for the deletion in the CMT1A gene.

Figure 29

The Value of Lumbar Puncture in Patients with CIDP

- Albumino-cytologic dissociation (i.e. high protein/normal cell count) is seen in 83-95% of patients with CIDP
- Elevated CSF protein is seen in 95% of patients with symmetric proximal and distal weakness in CIDP
 - **More mistakes are made where a phenotype which is not CIDP is called CIDP because of elevated CSF protein. Beware**
 - **Elevated CSF is > 60 or age, >100 in Diabetes**
- Elevated IgG synthesis
 - Reports suggesting IgG synthesis rate correlates with disease activity

References:
 • Faleck H, et al. Cleve Clin J Med 1989 Jul-Aug;56(5):539-541

Should a lumbar puncture be performed?

Another value that comes up frequently when evaluating patients with neuropathies is whether or not a lumbar puncture needs to be done in order to distinguish between CIDP and diabetes (Figure 29). In immune neuropathy such as CIDP, approximately 90% of the time there will be an albuminocytologic dissociation. The problem arises when the clinical phenotype is not the typical NP1 CIDP pattern. It is known that patients with typical diabetic neuropathy can have elevated CSF protein as well, but the presentation is usually an NP2 pattern. Therefore, if one did a CSF examination in a typical NP2 DSNP patient and found an elevated protein it would be a mistake to consider this CIDP and treat the patient with immunomodulating drugs. In other words, if the patient has a small amount of

toe weakness and numbness distally, a distal axonal sensory-motor neuropathy (NP2), and the CSF protein is 150 mg/dL, this does not mean the patient has CIDP just because of the elevated CSF protein. The patient does not have the pattern of weakness associated with CIDP-NP1. This is why you must be very cautious about over-interpreting spinal fluid protein values. Therefore, whether or not one obtains a CSF study should be based on the clinical pattern and the disease progression.

In addition, one needs to take age into consideration when evaluating CSF protein. CSF protein increases the more we age. For example, 60mg/dL is normal for a 60 year old.

In the evaluation of very chronic neuropathies, for example, over 10 years, it will be unlikely to find an

Figure 30

Potential Etiology	Tests To Order	Pattern
CIDP	CSF, NCS	NP1
Diabetes	Fasting glucose, HgbA1c	NP2
Impaired glucose tolerance	2 hour glucose tolerance test	NP2
B12 deficiency	Vitamin B12, methylmalonic acid	NP6, NP2
Paraproteinemia	Serum immunofixation, Quantitative Immunoglobulins, serum free light chains	NP1, NP2
CMT1	PMP duplication/ deletion, Cx32, MPZ	NP2
CMT2	EGR2, FIG4, GARS, GDAP1, HSPB1, LMNA, MFNA2, MFN2, MPZ, Periaxin, RAB7, RFC1	NP2
Hereditary amyloidosis	Transthyretin	NP2, NP3, NP10
Sjogren's syndrome	SS-A, SS-B	NP2, NP9, NP10
If tests are normal but there is marked progressive weakness	CSF, possible nerve biopsy	

Figure 31

Autonomic Neuropathies
<ul style="list-style-type: none"> • Cardiac, gastrointestinal, thermoregulation, pupillary abnormalities, sexual dysfunction • Often confused for IBS, fibromyalgia, malingering • Helpful to get autonomic testing to confirm presence of autonomic dysfunction <ul style="list-style-type: none"> • Can segregate POTS from Dysautonomia • Consider other objective tests of neuropathy <ul style="list-style-type: none"> • Gastric emptying study • Skin biopsy • Skin biopsy can be useful to look at small nerve fibers and at the innervation of the sweat glands

effective therapy (Figure 30). Nevertheless, an initial evaluation for chronic neuropathies is important. In the modern era, genetic testing plays more of a role than ever before. For this reason, it is important to pay attention to clues from the history and physical exams for a possible hereditary basis such as a family history of neuropathy, high arches, and hammer toes. One exception would be

hereditary amyloidosis for which genetic diagnosis testing for transthyretin mutations and therapy is now available. If a diagnosis still is not established after appropriate blood work and nerve conduction studies but the patient continues to deteriorate and have ambulation problems, then it might be reasonable to consider a CSF examination or a nerve biopsy.

Figure 32

Autonomic Neuropathies		
Potential Etiology	Tests to Order	Pattern
Acute autonomic ganglionopathy	Acetylcholine receptor ganglionic antibodies Voltage gated potassium autoantibodies GAD-65 Hu serology	NP10
GBS	CSF	NP1, NP10
Diabetes	Fasting glucose, HgbA1c	NP2, NP4, NP10
Primary Systemic Amyloidosis	Serum immunofixation, quantitative immunoglobulins, serum free light chains Tissue biopsy: skin, fat, rectal	NP2, NP10
Familial amyloidosis	TTR gene sequencing (Now FDA approved drug)	NP2, NP10
Sjogren's syndrome	SS-A, SS-B	NP2, NP9, NP10

We are seeing an increase in autonomic neuropathies in patients with cardiac, GI, thermoregulation, pupillary abnormalities, and sexual dysfunction (Figure 30, 31). These patients are often confused with IBS, fibromyalgia, and malingering. It can be difficult to tell the difference between patients who have autonomic disorders and patients who do not. If you have access to autonomic testing this is where this process should begin. If you do not have access to this testing, you can use a skin biopsy which can be useful to look at small nerve fibers as well as the sweat gland innervation involved in the autonomic nervous system. There are numerous causes.

Occasionally there is a need to order laboratory studies for a patient with fasciculations which are likely benign. In this situation, if the fasciculations are of great concern to the patient, a serum creatine kinase and an electromyogram to

reassure the patient they do not have motor neuron disease is reasonable. For patients with florid fasciculations and myokymia and in the setting of an NP2 neuropathy, voltage-gated potassium channel antibodies can be obtained to search for Isaac's syndrome, which can be paraneoplastic. Patients with Schwartz-Jampel syndrome have excessive muscle activity, particularly in axial and facial muscles, and on EMG have continuous motor unit high-frequency discharges. These patients have a characteristic "pinched" facial appearance with a tendency to keep their eyes closed due to hyperexcitable facial muscles. The diagnosis is made by finding a mutation in the *HSPG2* gene which codes for perlecan. Patients with stiff limbs due to unexplained upper motor dysfunction can be tested for glutamic acid decarboxylase antibodies found in stiff person syndrome (Figure 33)

Figure 33

Tests for Excessive Muscle Activity- NP11	
Occasional Fasciculations and/ or Cramps	Do nothing or CK/ EMG
Excessive fasciculations and/ or myokymia	Voltage-gated K channel antibodies
Above with pinched facies and skeletal deformities	HSPG mutation
Unexplained stiff limbs (upper motor neuron)	Serum glutamic acid decarboxylase antibodies

Figure 34

Laboratory Evaluation For Neuropathy Conclusions

- Differential can be based on history, exam , and the pattern
 - Don't allow EMG/NCV to confuse you
- Rationalize aggressive testing with aggressiveness of the disease process
 - Cryptogenic neuropathies are sensory and slowly progressive
 - A 10 year history will almost never ever be treatable.
 - If neuropathy is disabling and progressive than keep looking for cause
 - CSF: elevated protein, IgG synthesis rate would suggest a trial of empiric therapy
 - Nerve Biopsy
 - In face of progressive disease consider empiric trials of treatment
 - Most immune mediated neuropathies respond to steroids or IVIg within 3 months so don't flog a dead nerve and make the patient worse

References:
 • Levine T, Saperstein DS. Laboratory evaluation of peripheral neuropathy. *Neuro Clin NA*. 2013;31(2):363-376

In conclusion, differential diagnoses should be established by the history, exam, and by the pattern (Figure 34). Nerve conduction studies can be helpful but often be very confusing and if it does not correlate with what you are seeing in the history, the exam and the pattern always focus on the history, exam, and pattern when interpreting laboratory tests.

Aggressive testing needs to be rationalized against the aggressiveness of the disease. A patient who has a 10-year history of peripheral neuropathy which is slowly progressive and purely sensory is very unlikely to be able to be treated to stop the neuropathy from progressing. However, if the patient has pain that can be treated. On the other hand, if the neuropathy is progressive and disabling, causing

weakness and balance difficulties, that is where you want to be aggressive with spinal fluid and perhaps a nerve biopsy.

Response to immunosuppressive and immunomodulating therapy can be a diagnostic tool in itself. If IVIG or steroids are used the patient should respond within three months. If they do not respond, it is very likely that the presumptive diagnosis of an immune-mediated neuropathy is wrong, and that the patient most likely has an untreatable neuropathy.

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