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Peripheral Neuropathy: Not Just Diabetic Neuropathy

Peripheral Neuropathy, a condition characterized by malfunctioning of the peripheral nerves, is becoming more common or at least our ability to diagnose this problem is becoming more accurate. In a recent study, peripheral neuropathy has been found to be prevalent in approximately 2% of the population or even as high as 8% in populations over 55 years old.ⁱ In our office, on a regular basis, we see patients with varying symptoms from numbness and tingling to electrical shocks, burning or shooting pains. Many have diabetes (up to 30% of documented cases of neuropathyⁱⁱ), but many do not. All are being diagnosed in our office and sometimes diagnosed previous with peripheral neuropathy. Many patients without diabetes are told that they must have diabetes, because they have neuropathy. Are we doing a disservice to our patients by assuming it can only be diabetic neuropathy? If they have diabetes and peripheral neuropathy, is it always caused by their diabetes? Further, if it is always the same cause, why do the symptoms vary so drastically? Lastly, are there treatment options to alleviate the symptoms or even improve the neuropathy? As these questions are discussed, may we better serve our peripheral neuropathy patients with a better understanding of this unique diagnosis?

Causes of Peripheral Neuropathy

For many years a patient with peripheral neuropathy has been presumed to have diabetes or be an alcoholic. Since that time, it has been determined that there are no less than 100 different causes of neuropathy including diabetes most commonly (at least in the United States), leprosy common in 3rd world countries, and alcoholism only rarely in high risk individuals.ⁱⁱⁱ Diseases that affect nerves may have peripheral neuropathy as their only presenting symptoms. Other causes of neuropathy can include metabolic, autoimmune, hereditary, and infectious diseases with drugs, toxins or tumors also sometimes presenting with neuropathy.

With this understanding, is diabetes the cause of peripheral neuropathy? In a patient with diabetes, or in many individuals that are under diagnosed with diabetes or insulin resistance (pre-diabetes), diabetes may be the initiating factor but in many instances it isn't.^{iv} In the diagnostic process, other causes must be evaluated to facilitate better treatments and possible improvement of the causes and symptoms of peripheral neuropathy.

The Diagnosis of Neuropathy

In this diagnostic process, therefore, it is important to utilize physical exam and adjunctive testing with an accurate and complete history to obtain the diagnosis of neuropathy. In fact, neuropathy can easily be diagnosed, but it is often more difficult to identify a true cause of neuropathy.

The History: What can we learn about the condition?

In obtaining a patient history with neuropathy, family history and medical history are both of great importance. In fact, if the patient has a strong family history of painful feet (as in parents or grandparents) or even numbness to the feet, this often may provide a correlation with an inherited neuropathy. Likewise, there are several medications (such as Vincristine, Cisplatin, Metronidazole, INH, HIV medications, some blood pressure medications and others) or toxic substances (including nitrous oxide, industrial chemicals, and heavy metals – arsenic, lead, mercury, etc.) that can cause neuropathic symptoms, or even injury to the nerves.

Other key diagnostic history information can be obtained by classifying when the symptomatology presented. Acute presentations or even sub acute presentations may indicate infectious etiology or immune-mediated etiologies. Gradual or insidious onset are more consistent with inherited, idiopathic, metabolic, or toxic etiologies.

Varying Symptoms: What nerves are involved?

The intricate web of nerves that supply the body are made of multiple small and large fiber axons, all of which can be affected. Different pathologic processes can affect distinct anatomic areas or the associated nerves. The involvement of peripheral neuropathy may include motor, sensory and autonomic nerves. Neuropathies can also be generalized, focal or multifocal.

In a focal involvement, symptoms will be limited to a single nerve and its distribution. It is usually limited to focal compression (such as tarsal tunnel or carpal tunnel) or traumatic injury to a single nerve. Through careful evaluation during the diagnostic process and understanding of nerve distributions, these symptoms can be explained by a focal neuropathy.

In a multifocal involvement, some nerves are affected while others are spared. This is commonly related to infectious or inflammatory conditions as opposed to metabolic conditions. Involvement of the nerves of the face is typical of a multifocal neuropathy. Multifocal involvement may be more difficult to distinguish from a generalized distribution, but can be identified by a rigorous evaluation of symptoms.

Polyneuropathy or polyneuritis is the diagnostic term for a generalized nerve involvement where all nerves are affected. This usually presents as a symmetric neuropathy with involvement typically in the most distal and vulnerable nerves of the body, often called “stocking-glove distribution”. In this presentation, symptoms start at the toes and move proximal to the calves. The hands, whose nerves are typically the same length as the nerves to the calves, are often then affected as the neuropathy progresses proximal. Polyneuropathy is the most commonly encountered diabetic neuropathy.

In each of the involvements (focal, multifocal and generalized), motor and sensory nerves may be involved. Motor presentation will include weakness, muscle fasciculations, contracture of digits (as in hammertoes) or other foot deformities including the *intrinsic minus foot*. Sensory presentations will include numbness, tingling, electrical shocks, shooting pain and burning pain commonly, but may also include loss of coordination or balance. With both motor and sensory presentations, autonomic involvement may present as heart rate changes, blood pressure changes (especially with changes in position), swelling of the ankles, thinning of the skin, hair loss on the legs, delayed healing of the skin, ridged or brittle nails and/or loss of sweat or oil releases to the skin causing an increased dryness to the neuropathic foot. Some neuropathies will affect motor, sensory or autonomic nerves preferentially, but all three types may be affected to varying degrees causing a wide range of symptom presentations.

Lastly, selective vulnerability of the large or small fibers may produce varying symptoms. Some conditions present with large fiber involvement including loss of vibration and position sense, weakness and/or incoordination. Others conditions present with small fiber involvement and associated with spontaneous pain, insensitivity to painful stimuli and loss of temperature sensations. The extent of the neuropathy can either present as small fiber, large fiber or a combination neuropathy that can again produces a wide range of symptomatology.

Diagnostic Testing: Can we identify a cause?

With this understanding, it is imperative that we identify what nerves are involved and possible causes of the neuropathy. The more we know about the causes of the neuropathy, the better options we have for treating and improving neuropathy. The diagnostic testing options include:

Deep Tendon Reflex (DTR) including patellar reflex (L3), Achilles reflex (S1) or Babinski reflex (S1), can be utilized to evaluate large fiber neuropathy, especially muscular involvement.

Vibration Perception Threshold (VPT) utilizing a 128-Hz tuning fork or a biothesiometer (vibration meter) can test for large fiber neuropathy by testing the distal hallux. The biothesiometer allows quantitative measurements that can easily be reproduced. The VPT has a high predictive value.

Light Touch (Semmes Weinstein Monofilament) is probably the most utilized modality for neuropathy testing. The Semmes Weinstein 5.07/10g monofilament tests protective threshold including light touch and pain, both predictive of small fiber neuropathy.

Sharp & Dull Perception is also a simple examination technique for predicting small fiber neuropathy. An easy technique is utilizing a wooden cotton swab broken in half. The sharp side of the stick and the cotton swab are utilized in testing all dermatomes of the foot.

Hot & Cold Perception is another simple examination technique for predicting small fiber neuropathy. This is done by having a patient differentiate hot vs. cold, easily tested to the dorsum of the foot.

Nerve Conduction Velocity is the test of conduction speed of the nerves and often is indicative of large fiber neuropathy and can be utilized to evaluate spinal or compression etiologies. Peripheral neuropathy with small fiber etiology will often have a normal NCV test.

Epidermal Nerve Fiber Density (ENFD) is a new evaluation technique with high sensitivity and specificity for small fiber neuropathy. This test is performed in conjunction with specialized pathology labs (we utilize Bako Pathology Services) and is a great evaluation technique for the podiatric office.

Once the small fiber vs. large fiber designation is determined, laboratory testing can also be utilized to identify further causes of neuropathy.

Lab Tests:

Diabetes*	Blood Glucose, HgA1c
Pre-diabetes or Insulin Resistance*	Glucose Tolerance Test, Insulin Sensitivity Index (2 hour)
Vitamin B12 Deficiency*	CBC, Serum B12
Vitamin B6 Deficiency	Serum B6
Vitamin B6 Toxicity	Serum B6
Vitamin B1 Deficiency	Serum B1
Vitamin E Deficiency	Serum Vitamin E
Folate Deficiency	Serum Folate
Hypothyroidism	Thyroid Function
Heavy Metal Toxicity	Urine Heavy Metals

Other laboratory tests may include tests for HIV or other inflammatory or arthritic diseases, antibody tests for autoimmune causes and factors for various cancers. These are often less sensitive and specific for neuropathy.

**Most sensitive tests for common causes of neuropathy*

Treatment Options:

Can we decrease the symptoms?

Lyrica (Pre-gabalin) Effective treatment for symptoms including night pain, burning or electrical shocks. It is dose dependant and becomes more effective as dosage is increased. It is usually take twice a day morning and night and should start to be effective within 7 days. (Most common side-effect if encountered includes drowsiness.) Lyrica has been clinically proven to provide effective relief from the stabbing, burning and shooting pain of neuropathy and is currently one of two FDA approved medications for neuropathy.

Gabapentin (Neurontin) Effective treatment for symptoms including night pain, burning or electrical shocks. Patients have a tendency to “get used to” this medication and require a regular up dosing. High dosages are often required. It is usually taken 2-3 times per day. It takes several weeks often to notice improvement. (Significant side-effects are often encountered.)

Cymbalta (Duooxetine) A depression medication that is FDA approved for symptoms of neuropathy. This has been very effective in some individuals, especially with that depression commonly associated with neuropathy.

Amitriptyline Additional option for pain. Not as effective as Lyrica, but often more cost effective. Less side-effects than gabapentin.

Pain Medications Typically narcotic pain medications are ineffective at treating nerve pain, and are usually only take the edge off pain. The only pain medication with medical studies supporting its use in treating nerve pain is Ultram (Tramadol), a non-narcotic pain medication that has been shown to be less addictive. This may be considered if other treatments are ineffective.

Can neuropathy be improved?

Neuremedy: This is a medical food consisting of benfotiamine, that nourishes dysfunctional nerves allowing them to conduct impulses more normally. Since the early 1960s, benfotiamine has been used successfully to treat neuropathy in Asia and Europe. It has extensive studies that show it to be both effective and safe. It has recently been brought to the USA for treatment of neuropathy in our population.

Adequate blood levels of the micro-nutrient thiamine (Vitamin B1) are essential for the proper functioning of the nervous system. Recent studies have shown that many people suffering from peripheral neuropathy have low plasma levels of this essential micro-nutrient. They are unable to maintain adequate plasma thiamine levels through normal dietary means, or even through most of the B complex vitamins. They need a more bioactive form of thiamine for their nerves to function properly. In populations like diabetics, the elderly or neuropathy patients from other causes, Neuremedy alleviates the symptoms of peripheral neuropathy by delivering a highly bioactive form of the micro-nutrient thiamine to where it is needed, the nerve cells. Neuremedy works by nourishing the nerves.

Due to its overall efficacy, often people will experience improvement within 2-3 weeks of starting the treatments. It does not reduce the symptoms of neuropathy for everyone, but is definitely a viable options. Neuremedy is dosed at one capsule twice a day.

Metanx: This is a prescription medical food for the dietary management of endothelial dysfunction in patients with diabetic peripheral neuropathy. Traditional over-the-counter vitamins are synthetic forms of the nutrients found in nature and must be converted to their active forms before they can actually be used by the body's cells for such vital functions as DNA production, cell reproduction and homocysteine metabolism.

<u>B Vitamin</u>		<u>Active Form</u>
Folic acid	→	L-methylfolate (2.8mg)
Vitamin B ₆	→	Pyridoxal 5'-phosphate (25mg)
Vitamin B ₁₂	→	Methylcobalamin (2mg)

Metanx is a unique formulation providing the active forms of folate, vitamin B₆ and vitamin B₁₂ to manage the distinct nutritional requirements of neuropathy patients who often experience numbness, tingling, and burning sensations in their feet. Per studies run by the makers of Metanx, one tablet is equivalent to taking 19 folic acid tablets (1mg each), 2 B₁₂ tablets (1mg each), and 2 B₆ tablets (25mg each). You would need to take a handful of over-the-counter tablets to equal one dose of Metanx. Metanx is given at 1 tablet twice a day.

This area of neuropathy treatment is growing and the idea that "we can't do anything about it" is no longer true. Treatment options are available for patients with diabetes and those without. Next time you look at a patient complaining of nerve pain to their feet, think "What is the cause?" and you will do a greater service to these individuals.

ⁱ Michelle L. Mauermann and Ted M. Burns, **Pearls and Oysters: Evaluation of peripheral neuropathies** *Neurology* 2009;72:e28-e31

ⁱⁱ Norman Latov, MD, PhD and Anthony Sferruzza, PhD, **Laboratory Diagnosis of Peripheral Neuropathy**
http://www.questdiagnostics.com/hcp/intguide/jsp/showintguidepage.jsp?fn=CAP_LabDiagnosis_PeripheralNeurop.htm; updated 10/2008

ⁱⁱⁱ Latov, Norman. **Peripheral neuropathy: when the numbness, weakness, and pain won't stop**. Demos Medical Publishing LLC, 2007.

^{iv} Dyck P. In: **Horizons in Mayo Neurology and Neurosurgery: Perspectives on 100 Years and Future Trends**. Rochester, MN: 2006.