Pattern recognition of neuropathy and neuronopathy: 7 Questions / 11 Patterns

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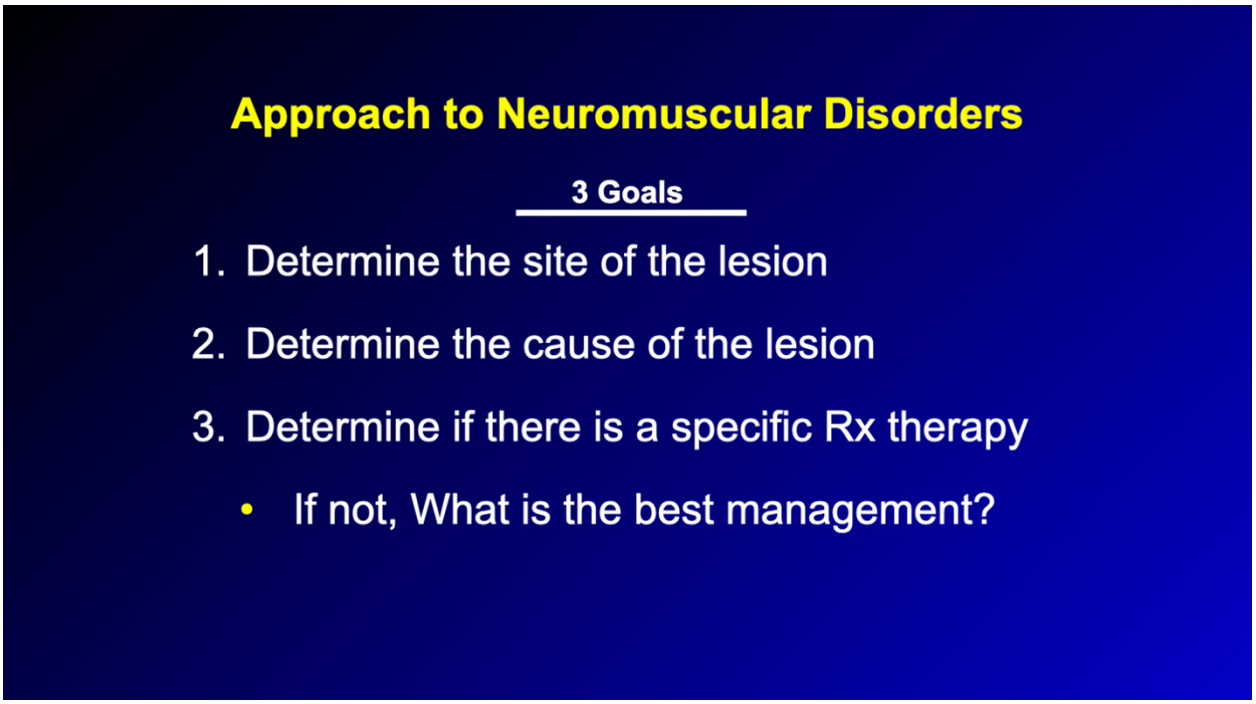
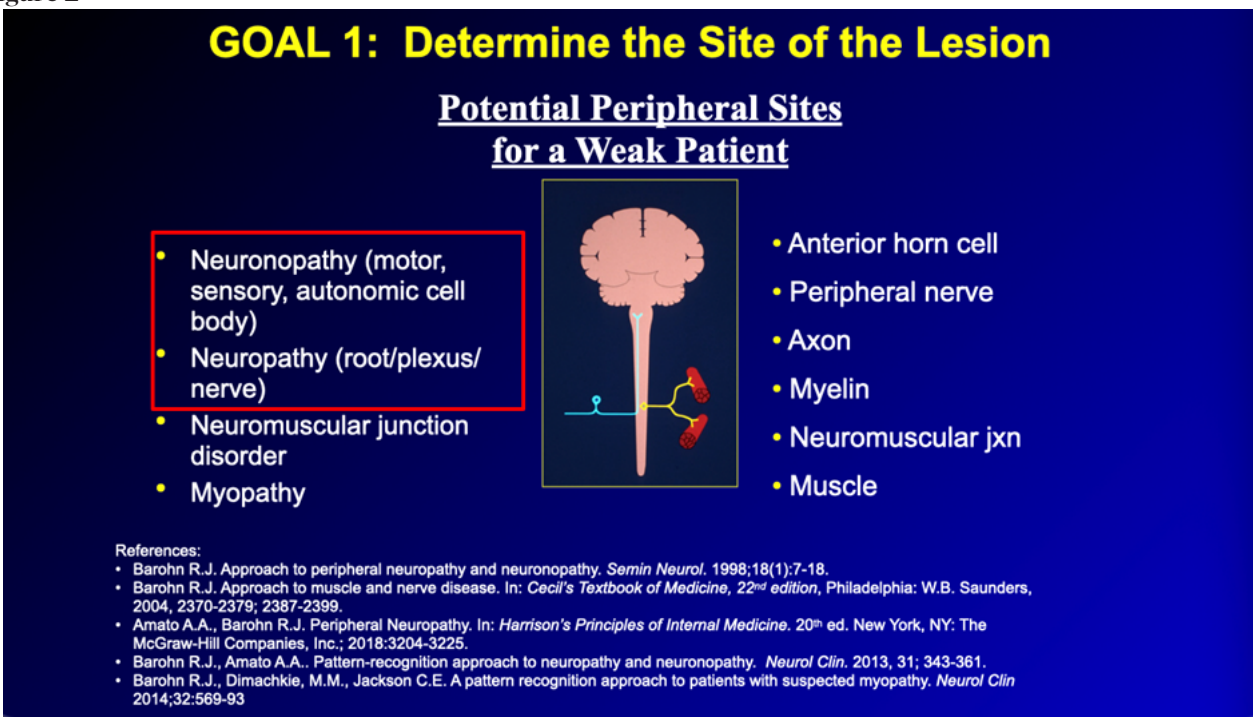
Every neurologist has three goals when they see a patient: 1. To determine the site of the lesion; 2. To determine the cause of the lesion; 3. To determine the specific therapy for the patient's problem and if not a specific therapy, what the best management is. (Figure 1)

Figure 1



This discussion will concern the peripheral nervous system components that include the lower neuron nerve cell bodies, roots, plexus, and nerves. (Figure 2)

Figure 2



Therefore, this includes both lower motor neurons (anterior horn cells) and sensory neuron cell bodies or the dorsal root ganglia.

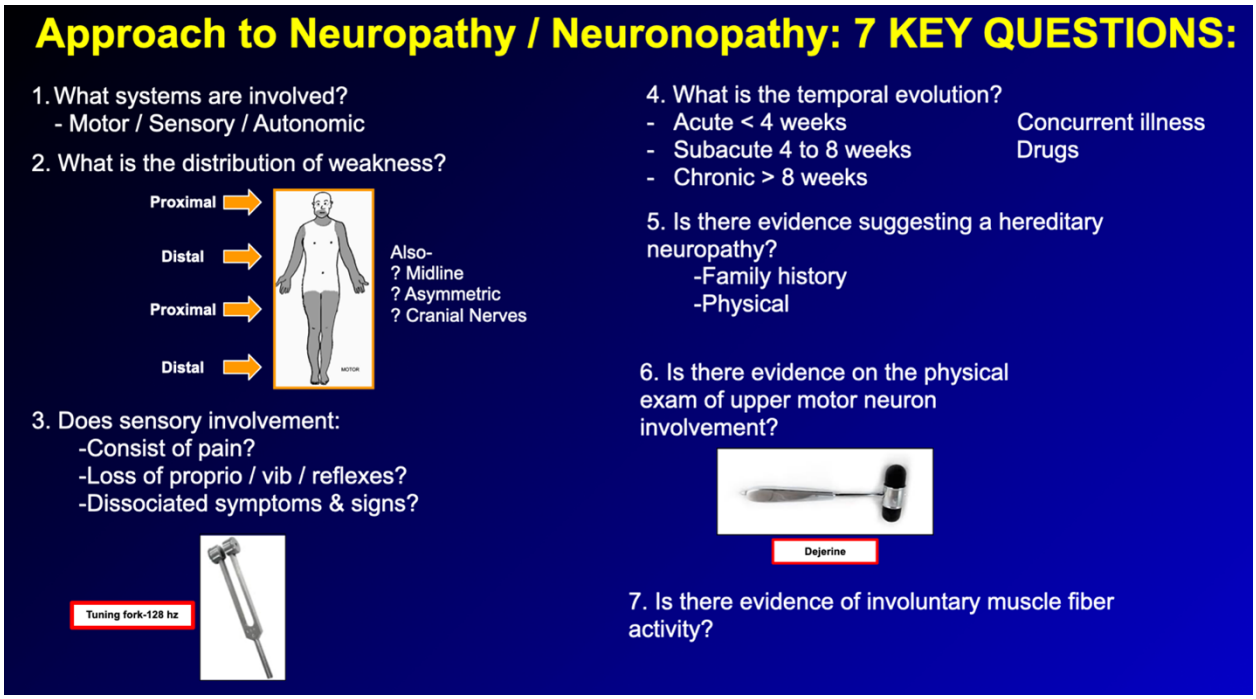
Using the pattern recognition approach to neuropathies and neuronopathies, clinicians can place a patient in a clinical pattern before ordering a single laboratory test.

In order to do that there are seven key questions that you need to be asking yourself when you take the history and when you do the physical exam. When you have the answers to these seven key questions, then you will put the patient into one of the patterns. Then after you put the patient into one of the patterns, it is time to think about ordering laboratory tests to finalize the diagnosis.

In previous publications and lectures, we taught the 6-question/10-pattern approach. We have now added question #7 on excessive muscle activity and created pattern 11 to accommodate some of these patients.

What are the **SEVEN KEY QUESTIONS** you need to answer to put the patient into a pattern? (Figure 3)

Figure 3



Question 1: What systems are involved?

When we ask, "What systems are involved?", what we are asking is if there is motor, sensory, or autonomic involvement. To determine if there is motor involvement you need to determine if the patient complaining of weakness. In addition, if the patient complains of muscle twitches or fasciculations, this could also indicate motor involvement. If there is sensory involvement, the patient will complain of numbness, tingling, pain, and poor gait or clumsiness.

If there is autonomic involvement, the patient will complain of lightheadedness when standing (orthostasis) or issues involving sweating, gastric motility, or impotence. Patients may complain of a combination of motor, sensory, and autonomic symptoms.

Question 2: What is the distribution of the weakness?

Once the patient says that they are weak, then you need to examine them and determine the distribution of the weakness.

Is the weakness exclusively distal, such as in an axonopathy or is it proximal and distal such as in an acquired myelinopathy? Is the weakness symmetric or asymmetric?

Does the weakness involve midline musculature such as cervical and thoracic paraspinous muscles, oropharyngeal muscles, other cranial nerve innervated muscles, and the diaphragm?

Question 3: What is the nature of the sensory involvement?

Question 3 further investigates sensory involvement and has several sub-questions. If the patient complains of numbness and tingling, then you know there is most likely sensory involvement. Additional questions regarding sensory involvement are as follows:

Does the patient have neuropathic pain?

If there is severe pain, then that will lead you down certain pattern pathways.

Also, if there is severe pain you know that you will need to treat the patient's neuropathic pain.

Next, you need to determine if there is severe proprioception loss, vibration loss, or loss of reflexes.

If the patient has numbness and tingling, and if proprioception, vibration, and reflexes are normal, then there is a possibility that this is a small fiber neuropathy. If vibration, proprioception, or reflexes are abnormal the neuropathy involves large fibers as well. If proprioception and vibration are severely involved, the lesion could also be either in the dorsal root ganglion or posterior columns.

Finally, are there **dissociated sensory symptoms and signs**?

The phrase "**dissociated sensory symptoms and signs**" may be unfamiliar to you.

The concept of dissociated cerebrospinal fluid findings in Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy (CIDP) with elevated protein and normal cell count is well known. This is a dissociated laboratory finding.

What do we mean by dissociated sensory symptoms and signs? The concept of dissociated sensory loss is sometimes a finding in cervical syringomyelia when due to a central cavity in the spinal cord, crossing spinothalamic pathways are disrupted causing pain and temperature loss bilaterally in the upper extremities with preservation of posterior column function. This has been termed dissociated sensory loss. But the concept of dissociated sensory symptoms and signs is a different concept and can be explained as follows:

When the patient presents with distal weakness (foot drop or hand weakness) and they do not complain of numbness and tingling, but on examination, you find a significant loss of either light touch, vibration, proprioception, temperature, or pinprick, that implies that there has been a long-standing disorder over many years and the etiology is most likely hereditary.

Question 4: What is the temporal evolution of the neuropathic disorder?

How fast or how slow is the condition progressing?

Acute is less than 4 weeks, chronic is more than 8 weeks, and subacute is 4-8 weeks.

This temporal framework comes from our understanding of Guillain-Barré syndrome which always evolves over less than 4 weeks and CIDP which by definition has to progress longer than 8 weeks.

But we use this temporal evolution to apply to all neuromuscular disorders and indeed it can be used for all neurologic disorders.

While we are considering the temporal evolution, we also want to know if the patient was exposed to any drugs that could cause neuropathic disorders, were they exposed to an infection that could have precipitated a neuropathic disorder, and do they have another underlying systemic condition that could predispose them to a neuropathic disorder.

Question 5: Is there evidence of a hereditary neuropathy?

To determine if there is a hereditary neuropathy, one needs to take a careful family history. In addition, on examination, one needs to determine if there are high arches, hammer toes, or scoliosis. One may have to examine family members as well. If there are dissociated sensory symptoms and signs as described above this strongly suggests a hereditary neuropathy.

Figure 4 shows a picture of three successive generations (grandmother bottom picture, mother middle picture, daughter top picture) of Charcot-Marie-Tooth disease patients demonstrating high arches and hammertoes that worsen as the patient ages.

Figure 4

Question 6: Is there evidence on the physical exam of upper motor neuron involvement?

Are there brisk reflexes, Hoffman's signs, any increased tone, or extensor plantar responses?

Question 7: Is there evidence of excessive muscle fiber activity?

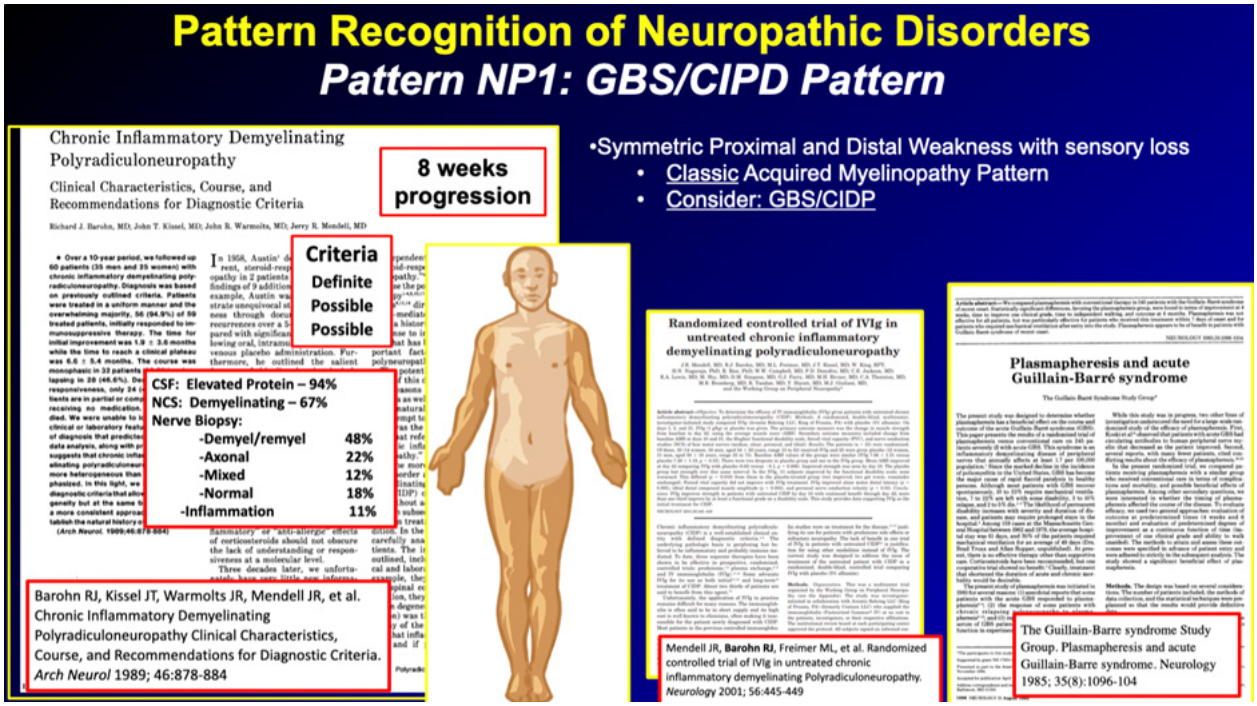
First, you should ask the patient if they have noticed muscle twitches. If the answer is "yes" then ask them which muscles have had twitches and how frequently they occur and what time of day. They can also ask if the twitches are exacerbated by exercise or drinking caffeine. Then, examine the patient once they have disrobed and carefully look for fasciculations. Sometimes fasciculations can be elicited by gently tapping a muscle with a reflex hammer or with the tip of the examiner's finger. More complex spontaneous muscle activity can be classified as myokymia. To classify an excessive muscle movement as myokymia it is necessary to do a needle EMG and determine if the spontaneous muscle activity is regular and periodic. Fasciculations are usually irregular and have no periodicity. Fasciculations can ultimately be benign in etiology or could indicate underlying nerve damage. Question 7 only addresses excessive muscle activity due to neuropathic disorders and not myopathic (see discussion below).

Once the answers to these seven key questions are obtained, you can place the patient into one of the **ELEVEN NEUROPATHIC PATTERNS.**

The **ELEVEN NEUROPATHIC PATTERNS** (NP) are as follows:

NP1: **Symmetrical, proximal, and distal weakness with sensory loss.** (Figure 5)

Figure 5

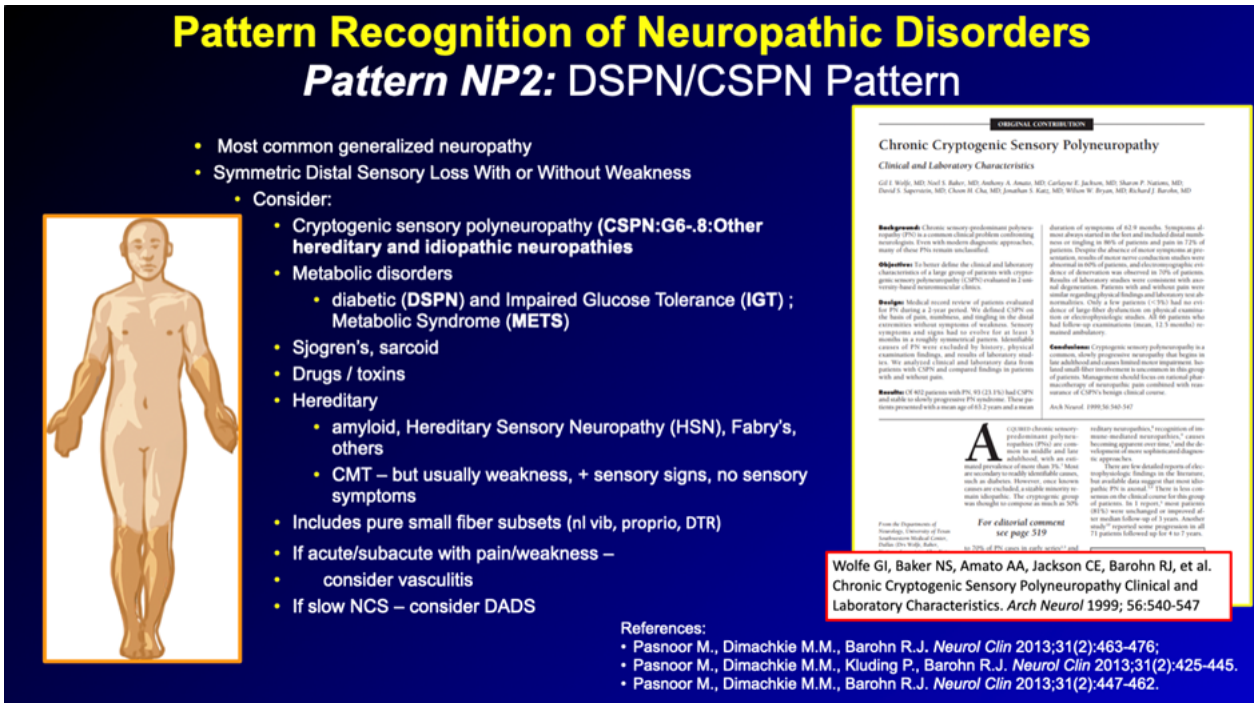


We also refer to this as the GBS/CIDP pattern. These patients have numbness, tingling, and weakness, and on examination, they have weakness in proximal and distal muscles.

It is extremely important to identify the NP1 pattern because it is the hallmark of classic acquired myelinopathy and is treatable with either immunomodulating or immunosuppressive therapy. While a temporal distinction is the primary determination between acute GBS (less than four weeks) and chronic CIDP (greater than eight weeks), there are other features that are more consistent with GBS such as significant autonomic and respiratory involvement.

NP2: **Symmetric distal sensory loss with or without weakness.** (Figure 6)

Figure 6



This is also referred to as the DSPN/CSPN pattern.

This is the most common generalized neuropathy pattern. In the NP2 pattern, patients often have no or very little weakness, although prominent distal weakness can occur. The most common causes of this pattern are diabetic sensory polyneuropathy (DSPN), or cryptogenic sensory polyneuropathy (CSPN). More recently, the metabolic syndrome has also emerged as a cause. We, therefore, believe this pattern also occurs in metabolic syndrome and painful neuropathy associated with impaired glucose intolerance.

Other causes of this pattern are toxicity from drugs or other toxins.

Hereditary neuropathy, also known as Charcot-Marie-Tooth disease (CMT) also falls into this category. However, in hereditary neuropathy, the weakness is out of proportion to the sensory involvement as noted above.

Amyloid neuropathy, both hereditary and acquired, can have an NP2 presentation. Hereditary or familial amyloidosis is very important to recognize because we now have treatments for this disorder.

We group all small and large fiber neuropathies in the NP2 pattern.

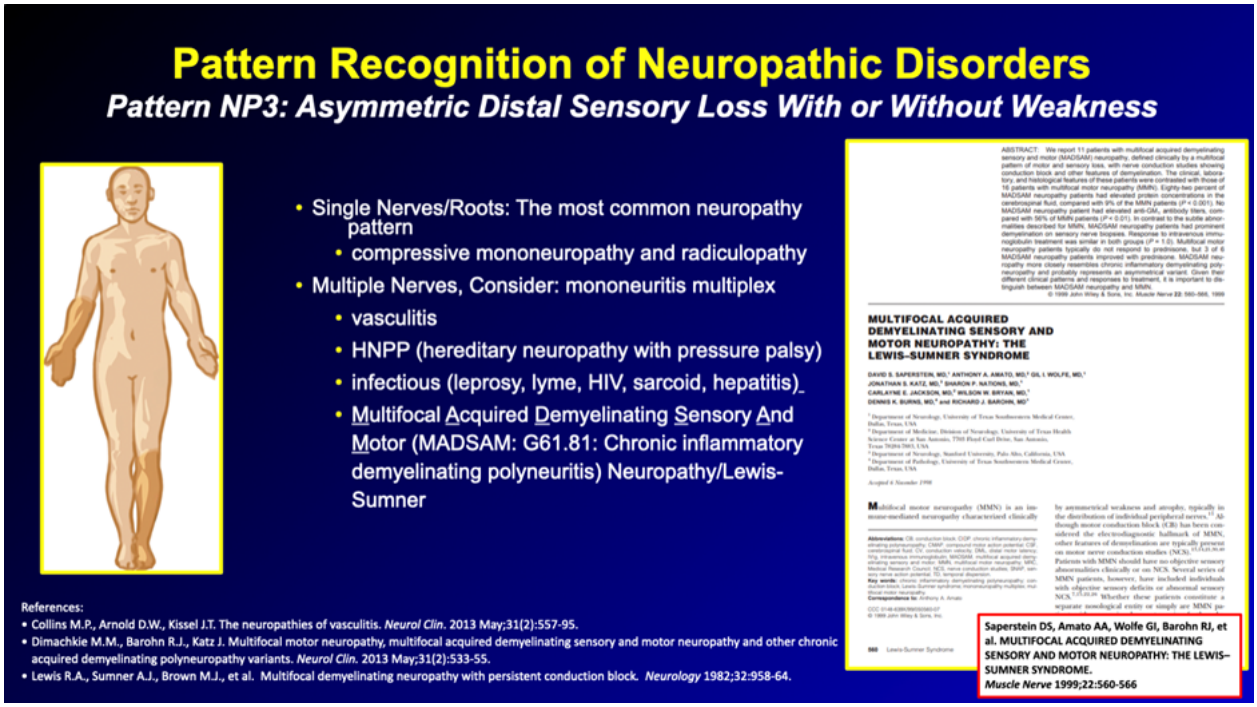
Based on the clues from the physical exam you will determine if the patient is likely to have a small fiber neuropathy, as noted above. Then, laboratory tests such as nerve conduction studies and skin biopsies can further support the clinical impression that only small fibers are involved.

Usually, vasculitis presents as mononeuritis multiplex (see NP3 below) but rarely, vasculitis presents with an NP2 pattern. When this occurs, there is usually intense pain, significant distal lower extremity weakness with sensory loss, and the temporal evolution is more often acute or subacute.

In addition, while most chronic acquired demyelinating polyneuropathies have an NP1 pattern, one variant called distal acquired demyelinating symmetric neuropathy (DADS) will have an NP2 pattern.

NP3: Asymmetric distal sensory loss with or without motor weakness (Figure 7).

Figure 7



This is the most common neuropathy when it is a single nerve or root.

Examples are median neuropathy at the wrist, ulnar compressive neuropathy, peroneal compressive neuropathy, or a cervical or lumbar radiculopathy (ex., C5, C6, L5, S1).

On the other hand, if two or more distal peripheral nerves are involved, then that is mononeuropathy multiplex.

It is important to recognize mononeuritis multiplex quickly as one of the causes is vasculitis which is serious and can be life-threatening.

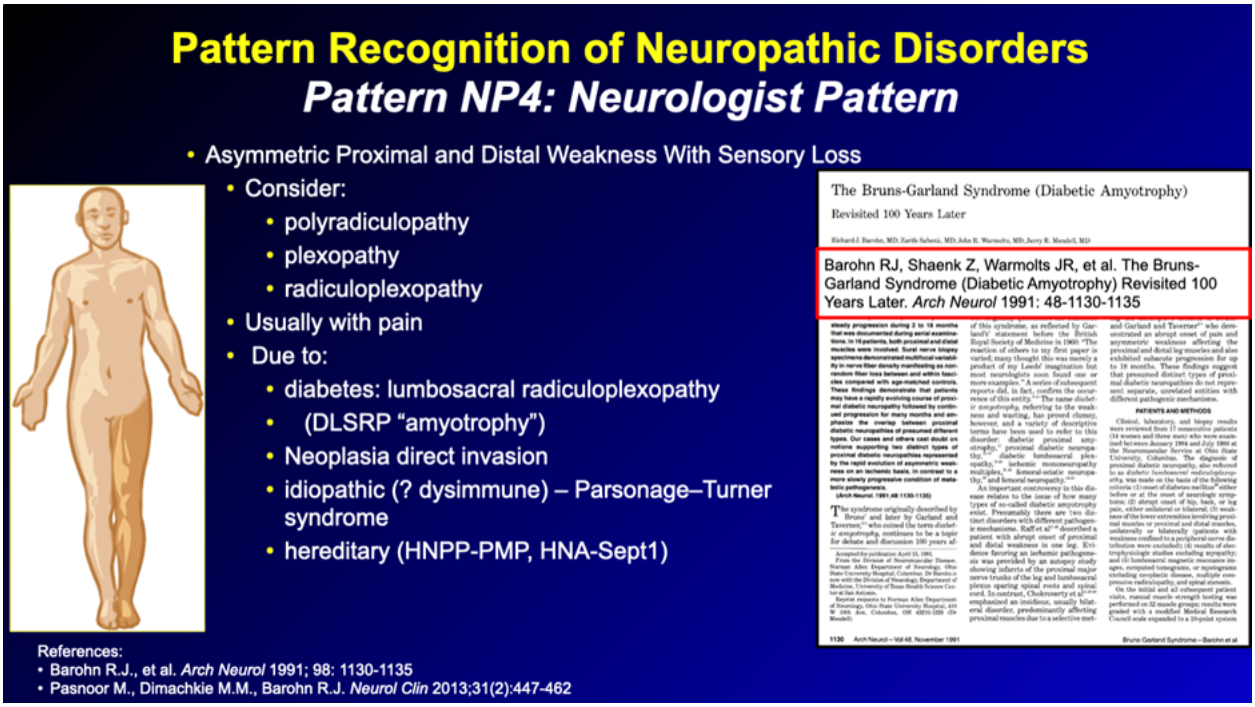
Vasculitis typically occurs subacutely or acutely. There also is a hereditary form of mononeuropathy multiplex, hereditary neuropathy with liability to pressure palsy (HNPP) which evolves over months or years with different episodes of compressive neuropathy.

A variety of infectious diseases can produce mononeuropathy multiplex in which case it is then referred to as mononeuritis multiplex (Figure 8).

There is another variant of chronic acquired demyelinating neuropathy that presents with mononeuritis multiplex and that presents multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), this is also referred to as the Lewis Sumner syndrome. This is another CIDP variant.

NP4: **Asymmetric proximal-distal weakness with sensory loss** (Figure 8).

Figure 8



We call this "The Neurologist's Pattern" because it is usually the neurologist who makes the diagnosis after others have incorrectly diagnosed the patient.

The key distinguishing variable that distinguishes NP3 from NP4 is the presence of **proximal** weakness in NP4.

Patients will present with an entire arm or leg involved, proximally and distally, from nerve roots C5 to T1 or from L1 to S1.

All of these segments do not have to be equally involved but both proximal and distal muscles are involved to some extent. When this occurs, the lesion has to be in either multiple roots, (polyradiculopathy) or in the plexus, or in both-radiculoplexopathy.

These patients usually have severe pain at the onset.

The most common cause of NP4 is diabetes and therefore we call this diabetic lumbosacral radiculoplexopathy. In the older literature, it was called diabetic amyotrophy, but we do not use that term any longer as it is nonspecific and simply implies loss of muscle mass in a diabetic. Another term for diabetic lumbosacral radiculoplexopathy (DLSRP) that we have used in the past is Bruns-Garland syndrome (Figure 9).

Usually, the patients have been misdiagnosed and they may have had back surgery for presumed compressive radiculopathy, but they are still getting worse.

The neurologist often will then be consulted after lumbar surgery and make the diagnosis of DLSRP. Hence, as noted above, we call this "The Neurologist's Pattern".

Other causes of NP4 are neoplasia, either direct invasion into the plexus or the meninges (either carcinomatous meningitis or lymphomatous meningitis).

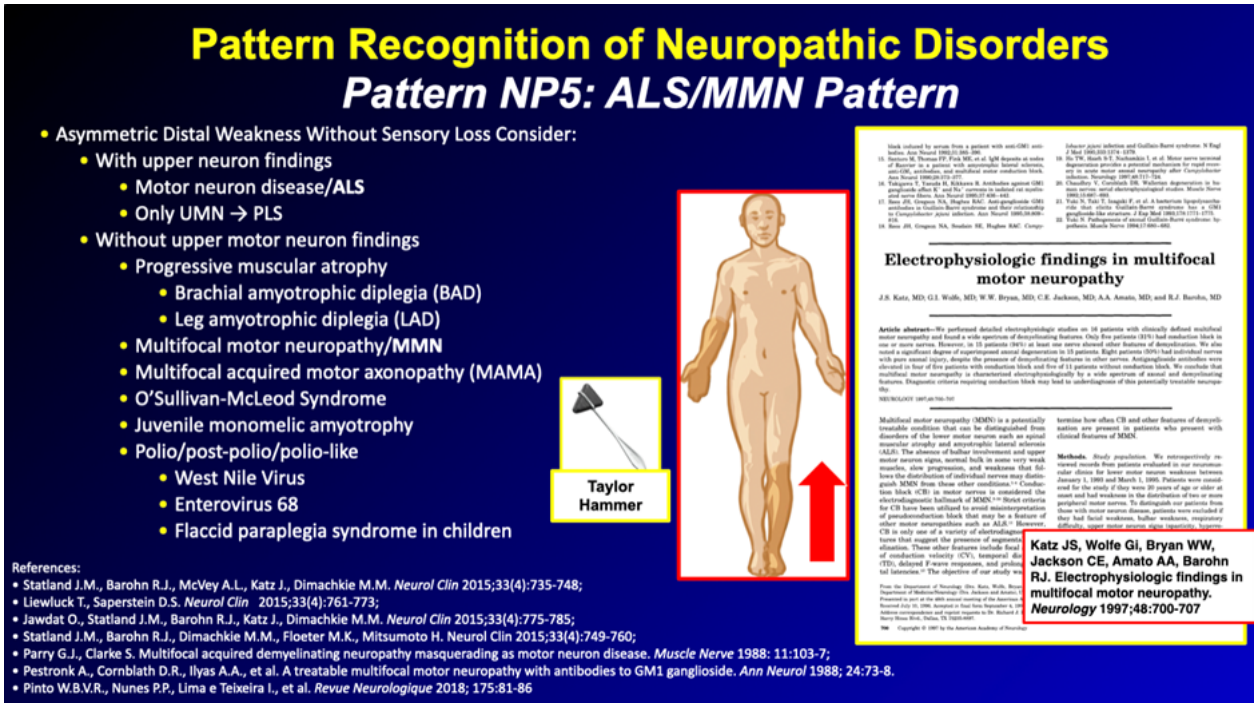
Other causes of NP4 are idiopathic or immune-mediated such as the Parsonage-Turner Syndrome that occurs in the brachial plexus.

There is also a lumbosacral idiopathic variant as well.

There are also hereditary causes of plexopathy due to hereditary neuralgic amyotrophy (HNA) related to SEP9 mutations. SEP9 mutations account for approximately 50% of HNA and other gene mutations have been identified with this phenotype. These are generally autosomal dominant. HNPP can occasionally present with a painless recurrent plexopathy. Hereditary plexopathy cases generally are painless in contrast to acquired cases which are usually painful.

NP5: Asymmetric distal weakness without sensory loss (Figure 9)

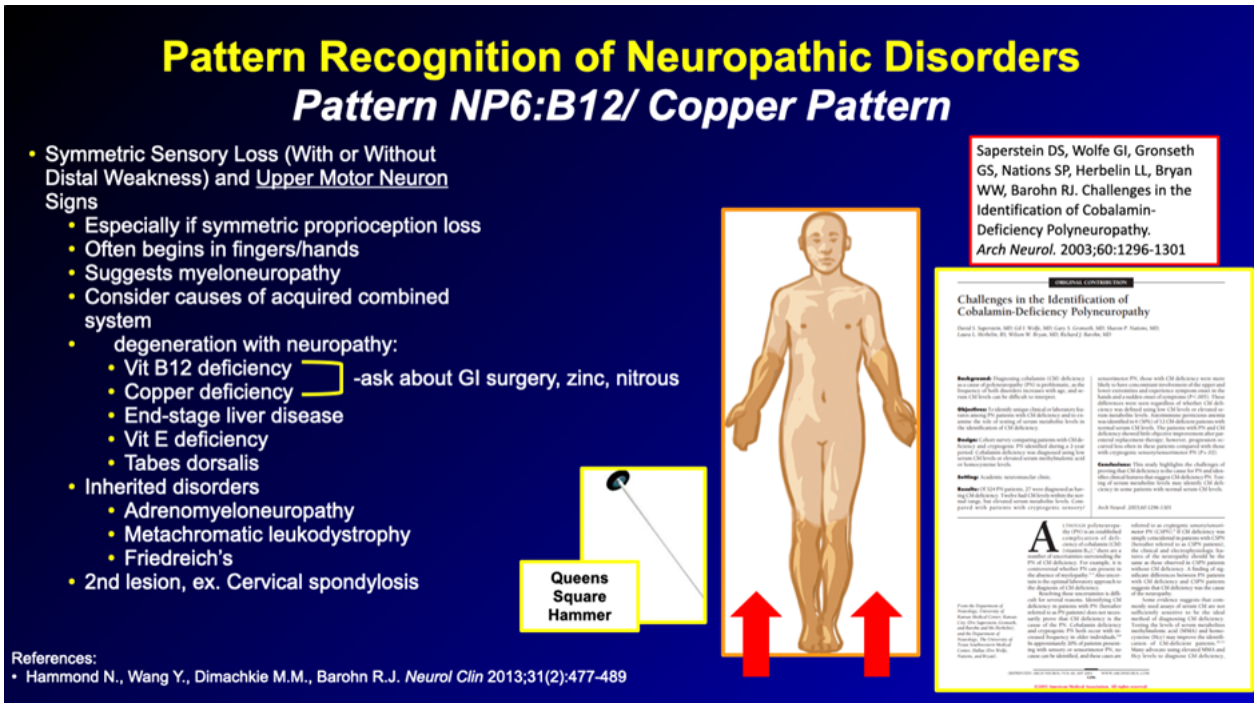
Figure 9



NP5 is also known as the "ALS/MMN pattern". With this pattern, the patient presents with progressive foot drop or progressive hand weakness typically for six to twelve months. There are no sensory symptoms or signs. After you have established that the patient is weak in this distribution then you need to assess for upper motor neuron signs. You need to determine if there are hyperactive reflexes or increased tone or pathologic reflexes. If they have upper motor neuron signs the diagnosis is almost always going to be amyotrophic lateral sclerosis (ALS). Occasionally, with exclusively upper motor neuron signs the diagnosis can be primary lateral sclerosis (PLS). ALS is much more common than PLS. If they do not have upper motor neuron signs, then the differential diagnosis is more challenging. The patient could have progressive muscular atrophy (PMA) which is the lower motor neuron form of ALS. If the weakness begins in one hand, the diagnosis could be multifocal motor neuropathy, which is treatable. There are a few other diagnoses that can present with this pattern such as juvenile monomelic atrophy, polio or polio-like viruses that can cause weakness, and multifocal acquired motor axonopathy, which we call MAMA.

NP6: Symmetric sensory loss with or without distal weakness and upper motor neuron signs. (Figure 10)

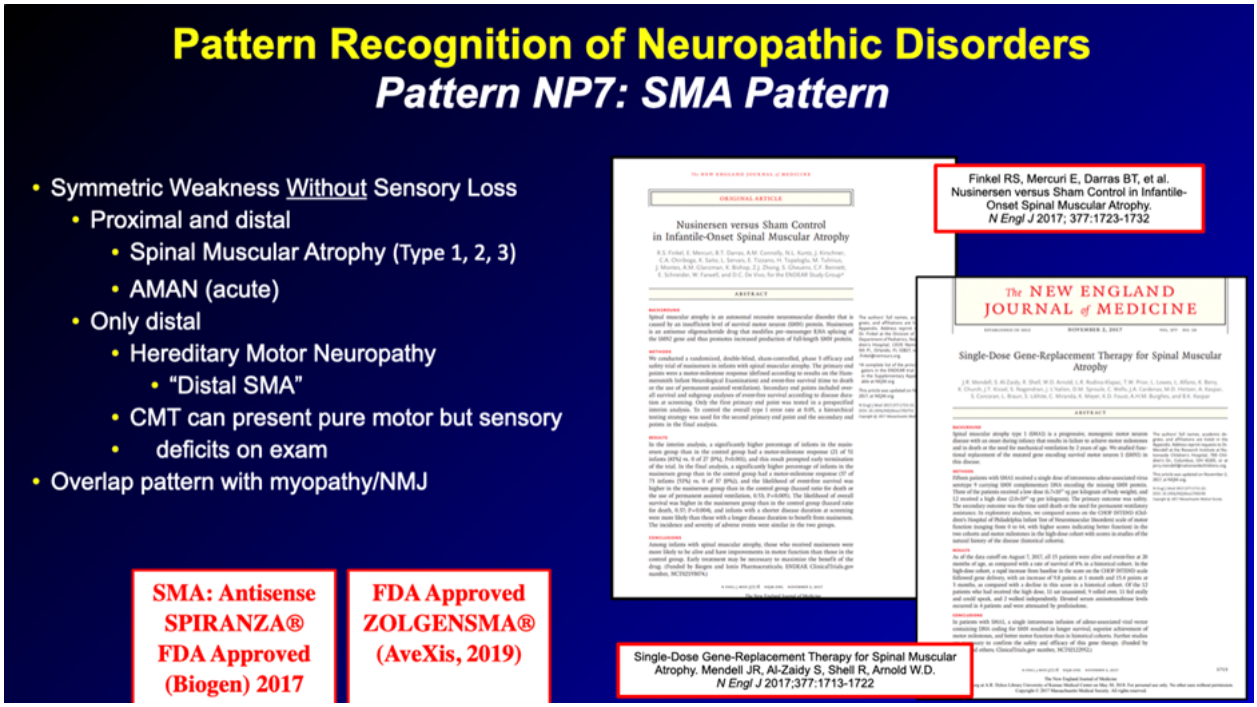
Figure 10



This is similar to the NP2 but with upper motor neuron signs. The patient presents with numb hands and feet. Sometimes the sensory symptoms can begin in the hands before the feet. They have significant gait instability, and they have significant proprioceptive and vibration loss, more than is seen in a typical DSPN or CSPN patient. They have brisk reflexes, pathologic reflexes, and they may have increased tone. All of these features in combination suggest myeloneuropathy. Both the peripheral nerves and the spinal cord are involved. That is why these sensory symptoms can begin in the hands and also why there is extensive proprioception and vibration loss due to posterior column damage. The patient may not have all of the abnormal symptoms and signs noted above and the evidence of upper motor neuron signs could be subtle. Therefore, a high index of suspicion is indicated. For example, the patient with a typical NP2 pattern may have a loss of ankle reflexes but have crossed adductor reflexes at the knees and Hoffman's reflexes in the fingers. Or the patient may have an NP2 pattern with easily obtainable ankle reflexes, crossed adductors, and Hoffman's signs. Any of these combinations would put the patient in the NP6 category. The next step is to search for combined system generation due to B12 and/or copper deficiency. Therefore, you have to ask about prior gastrointestinal surgery, excessive zinc use, and illicit nitrous oxide use. Other rare entities that can have a combination of upper and lower motor neuron signs with motor and sensory involvement include inherited disorders such as Friedreich's ataxia, adrenomyeloneuropathy, and metachromatic leukodystrophy. On the other hand, the NP6 pattern can also be produced when a second lesion is superimposed on CSPN or DSPN, such as cervical spondylosis or bilateral strokes. Therefore, these patients usually have to have MRI imaging of the cervical spine and the brain to exclude second lesions.

NP7: Symmetric weakness without sensory loss. (Figure 11)

Figure 11

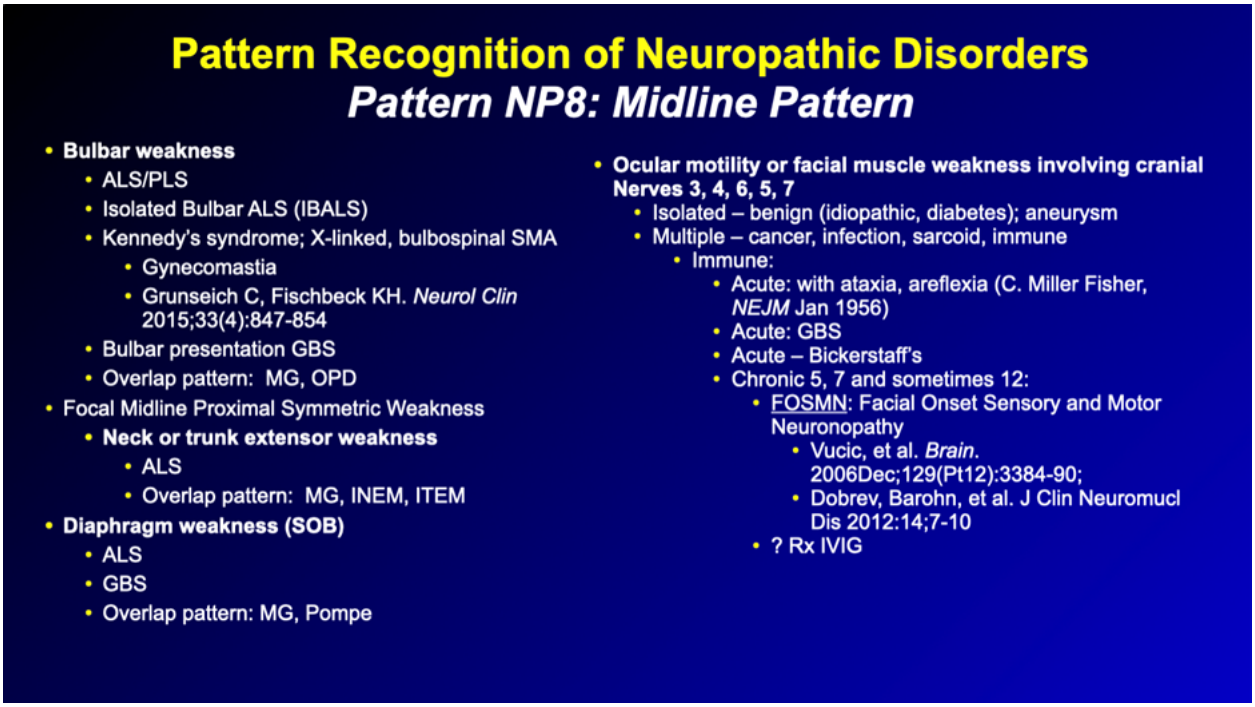


In the NP7 pattern, the weakness is usually proximal and distal and when this occurs, the diagnosis is usually spinal muscular atrophy (SMA), either type 1, 2, or 3. This is extremely important to recognize as autosomal recessive SMA is now treatable with gene therapy and antisense therapy. While SMA can present at birth or shortly after birth it is considered a chronic condition. On the other hand, if this pattern occurs acutely in either adults or children, the diagnosis may be acute motor axonal neuropathy (AMAN). If the presentation is chronic and only distal, then we refer to this entity as hereditary motor neuropathy. In the older literature hereditary motor neuropathy was referred to as distal SMA.

NP7 overlaps with myopathic and neuromuscular junction patterns which can present with proximal and distal weakness with no sensory loss.

NP8: The Midline Pattern (Figure 12)

Figure 12



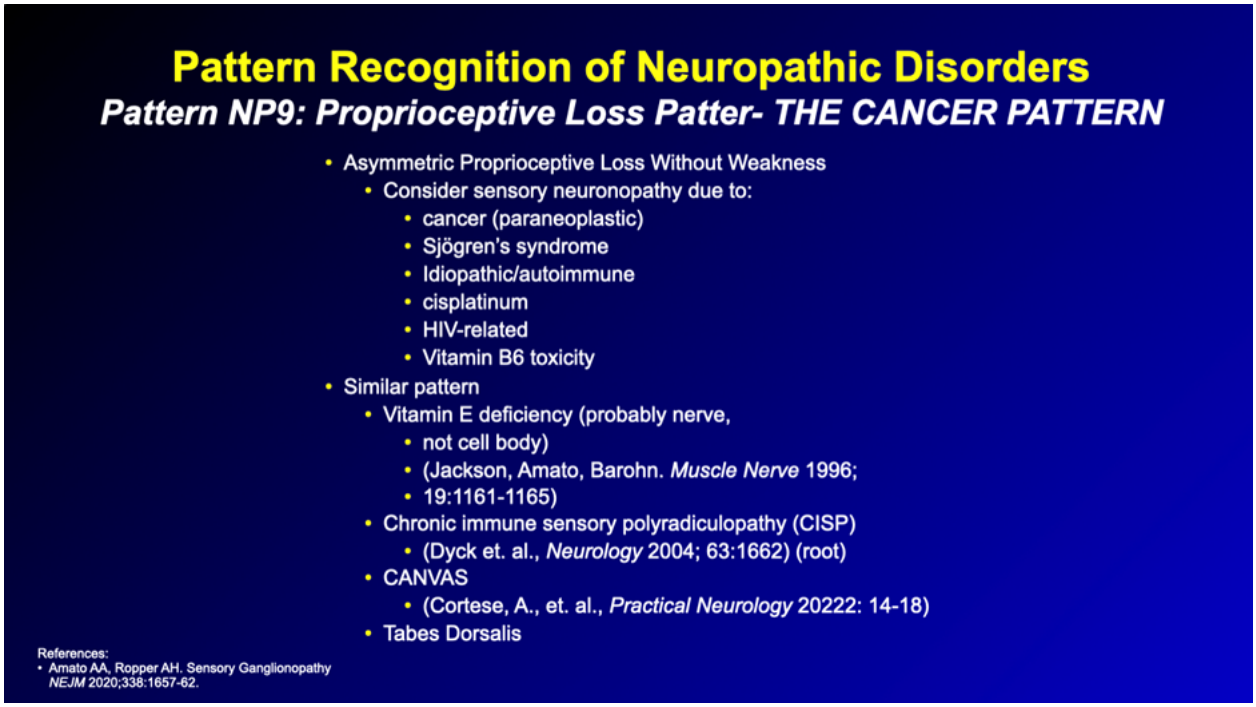
The "midline pattern" term is used when there is weakness of midline muscles involving bulbar or cervical or thoracic musculature, or the diaphragm. When a neuropathic patient presents with chronic progressive bulbar weakness the diagnosis is most likely going to be ALS, PMA, or PLS. Alternatively, it could be Kennedy's syndrome, X-linked bulbospinal SMA. If it is an acute presentation the diagnosis may be a bulbar presentation of GBS. Also in the midline pattern are patients who present with neck or trunk drop. When it is neuropathic, the most likely cause is motor neuron disease, ALS, or PMA. If they present with progressive shortness of breath over months ALS is a consideration and if it occurs acutely then GBS is a consideration.

Also included in the midline pattern are muscle disorders involving ocular motility or facial musculature. In other words, any disorder involving cranial nerves the oculomotor nerve (cranial nerve 3), trochlear nerve (cranial nerve 4), abducens nerve (cranial nerve 6), or facial nerve (cranial nerve 7). Most of the time individual cranial nerve disorders involving these nerves are benign and often idiopathic and they improve over time. Multiple cranial nerves can be involved in Guillain-Barré syndrome. When multiple cranial nerves are involved subacutely or chronically and the disorder is progressive this could be due to an underlying malignancy or infectious process. Occasionally, multiple cranial nerves are due to an idiopathic condition called facial onset sensory and motor neuropathy, also known as FOSMN. These patients present with numbness beginning in the lower face and oral cavity that progresses over several years to involve the scalp, neck, shoulder, and arms. The muscles of the facial nerve (cranial nerve 7) and hypoglossal nerve (cranial nerve12) are involved and eventually, the patients develop dysphagia due to involvement in the glossopharyngeal nerve (cranial nerve 9) and the vagus nerve (cranial nerve 10).

NP8 midline patterns can overlap with myopathic and neuromuscular junction patterns. For example, bulbar weakness occurs in myasthenia gravis and oculopharyngeal muscular dystrophy (OPMD). Also, neck and trunk weakness can be a prominent feature of myasthenia gravis, isolated neck extensor myopathy (INEM), and isolated trunk extensor myopathy (ITEM). Finally, both myasthenia gravis and myopathies such as Pompe disease can have predominant diaphragm weakness causing shortness of breath.

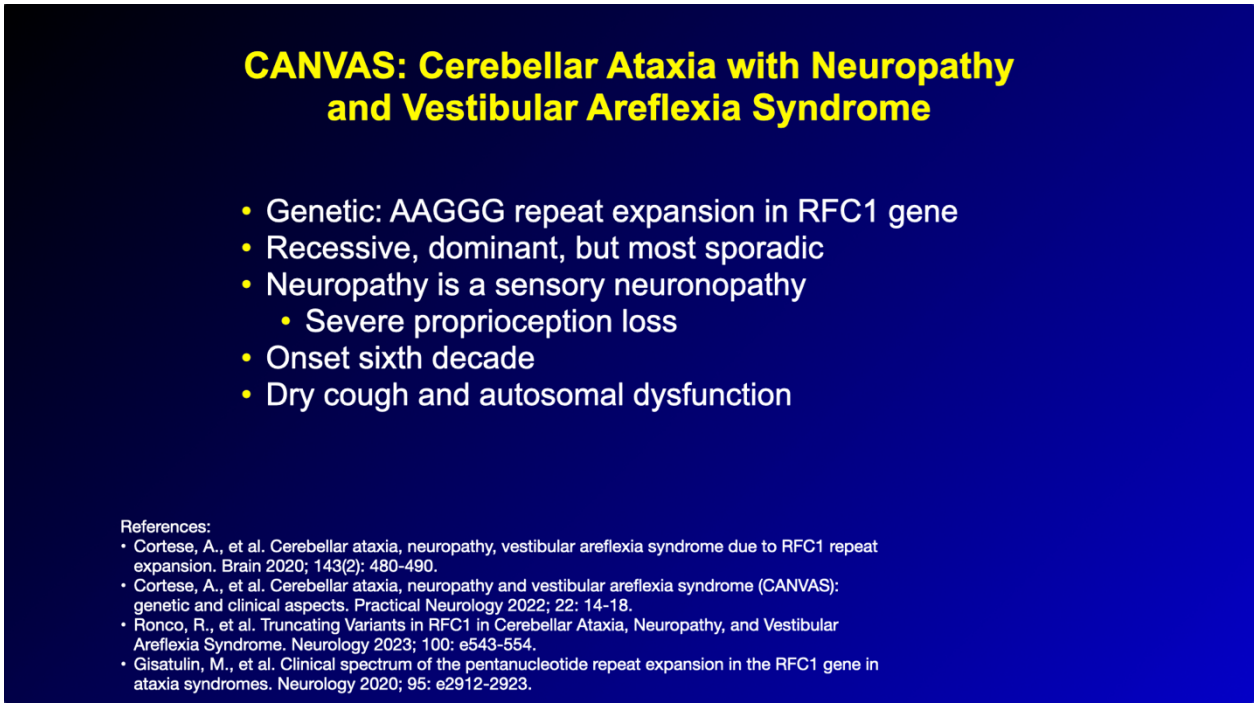
NP9: Asymmetric proprioceptive loss without weakness. (Figure 13)

Figure 13



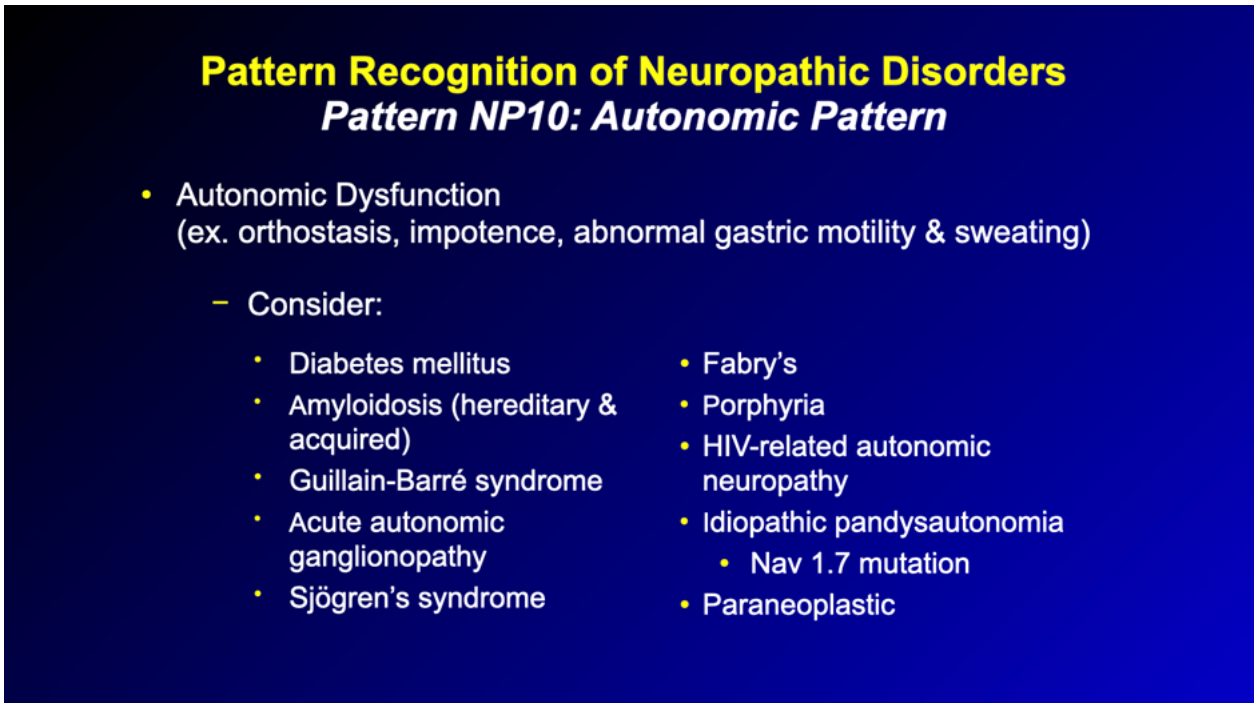
This is often due to an underlying malignancy with a paraneoplastic presentation. Therefore, we refer to this as "The Cancer Pattern". These patients present with numbness and tingling in either one leg or one arm or poor control of that limb which is due to proprioceptive loss. When you examine the patient, in addition to decreased touch and pin sensation, they have severely decreased proprioception either at the toes, ankles, and knees or the fingers, wrists, and elbows. When this occurs, the lesion is in the dorsal ganglion and the most common cause is cancer. Causes other than cancer include an autoimmune disorder such as Sjogren's disease. There may be other autoimmune causes of this pattern that may be associated with newly discovered antibodies to FGFR-3 and TS-HDS. Vitamin E deficiency neuropathy, either acquired or hereditary, can have the NP9 pattern. Another variant of CIDP, chronic immune sensory polyradiculopathy (CISP) presents with a classic NP9 pattern. CISP is presumably due to inflammation and demyelination of the sensory roots proximal to the dorsal root ganglion, and it is potentially treatable with IVIG. Some of these patients reportedly respond to intravenous immune globulin therapy, however, 2 small randomized, placebo-controlled trials showed no benefit from IVIG. CISP and sensory neuronopathy can clinically look very similar. The way to distinguish them is by the sensory nerve conduction studies which are preserved in CISP and abnormal in sensory neuronopathy. Other considerations with this pattern are toxicity due to drugs such as the platinums. HIV infection has been associated with neuropathies that have this pattern. A new entity has recently been described called CANVAS- cerebellar ataxia, neuropathy (most likely a neuronopathy), and vestibular dysfunction. This is due to a genetic defect in the RFC1 gene with a repeat expansion of AAGGG. These patients have severe proprioceptive loss and ataxia for multiple reasons including sensory neuronopathy. One of the clues to diagnosing these cases is that patients have recurrent coughing for which no etiology has been found.

Figure 14



NP10: The Autonomic Pattern (Figure 15)

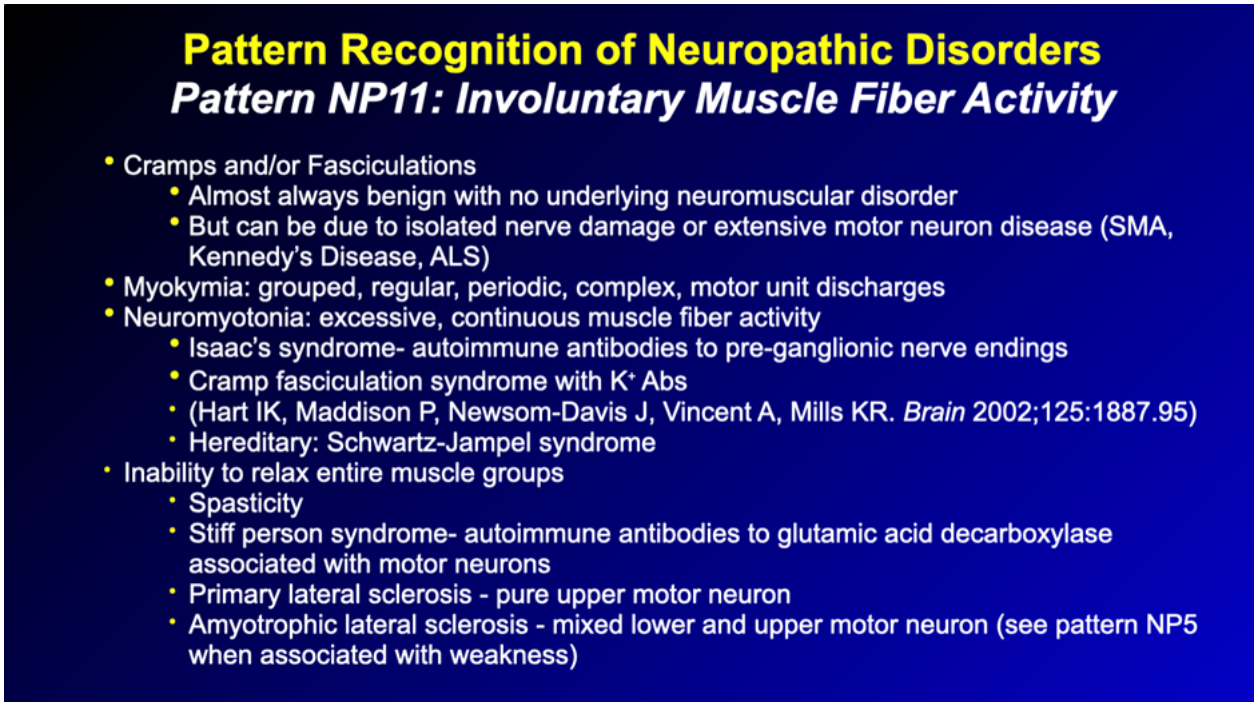
Figure 15



With the autonomic pattern patients present with orthostasis, impotence, abnormal gastrointestinal motility, and abnormal sweating symptoms. The most common cause is diabetes. But there are other causes such as hereditary amyloidosis and it is important to recognize this entity because it is treatable. Acutely, Guillain-Barré syndrome can have significant autonomic symptoms and signs.

NP11: Excessive muscle activity. (Figure 16)

Figure 16



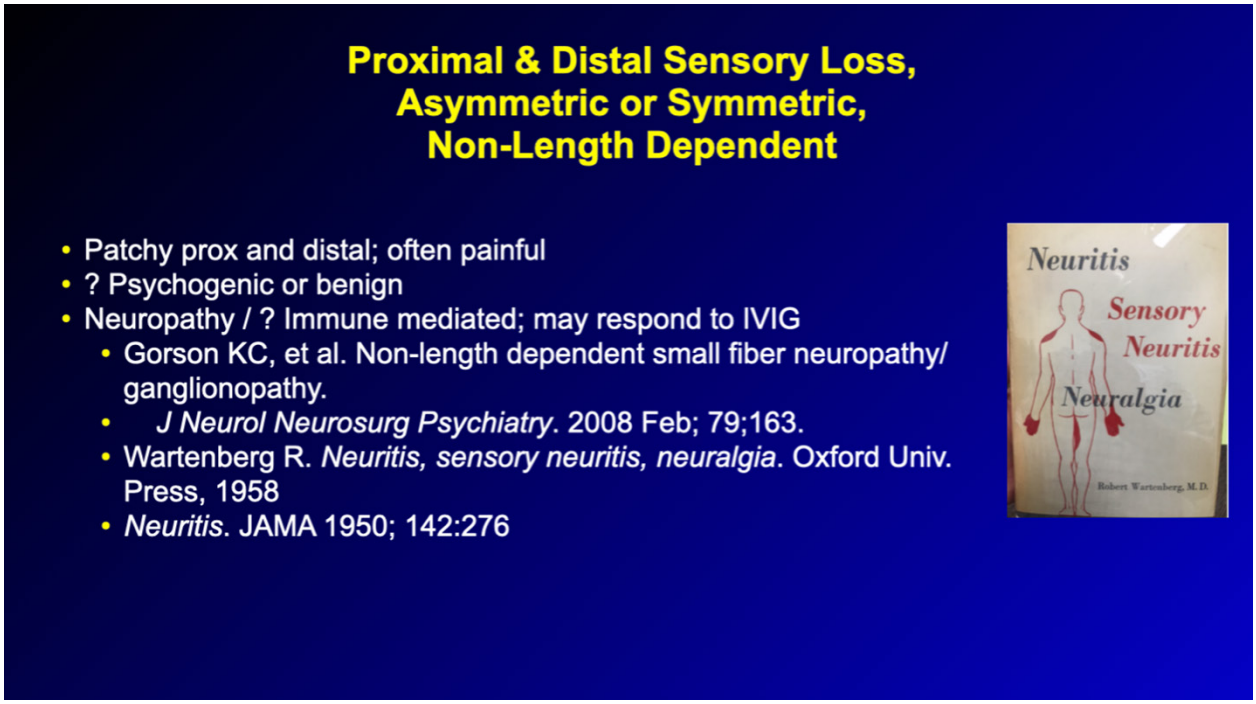
There are a variety of types and etiologies of excessive muscle activity that range from benign to ominous. Most fasciculations are indeed benign and do not represent any underlying medical problem or diagnosis. It is very common to experience muscle twitches and to visibly see them, particularly in the calf muscles such as the gastrocnemius, arm muscles such as the deltoid or biceps, or facial muscles such as the orbicularis oculi. These can occur when an individual is overly fatigued, after exercise, or after drinking an excessive amount of caffeine. Pyridostigmine for myasthenia gravis commonly causes fasciculations in the extremities and facial muscles. On the other hand, fasciculations can occur as a result of many types of peripheral nerve damage. This can be due to a relatively simple median nerve damage from carpal tunnel syndrome. Fasciculations can also occur in multiple skeletal muscles as a result of motor neuron disease from spinal muscular atrophy or amyotrophic lateral sclerosis. More complex, repetitive, and regular muscle twitches are often termed myokymia. However, determining the regular periodicity of myokymic twitches usually requires a needle EMG examination. Myokymia also can be the result of median nerve damage in carpal tunnel syndrome. Myokymic potentials can also occur after radiation therapy for cancer in muscles that are exposed to the radiation window. For example, radiation to the neck as a treatment for head and neck cancers can produce a brachial plexopathy with myokymic potentials in arm muscles. More dramatic excessive and continuous muscle fiber activity can produce what has been called neuromyotonia. Neuromyotonia can superficially look like multiple fasciculations, but a needle EMG examination will reveal the characteristic high-frequency neuromyotonic discharges. Neuromyotonia is usually the result of an autoimmune process at the presynaptic nerve endings and is due to antibodies directed to presynaptic potassium channels. This is also called Isaac's syndrome. The Schwartz-Jampel syndrome due to a mutation of the HSPG2 gene which codes for perlecan is a hereditary disorder that can produce an unusual continuous muscle fiber activity and muscle stiffness. This rare autosomal recessive disorder appears to cause an instability of neuromuscular junction transmission causing continuous muscle discharges. Therefore, while it is considered to cause a form of continuous muscle fiber activity it is probably better categorized as an unusual muscle-based myotonic disorder rather than neurogenic muscle stiffness. This entire category can be considered to overlap with muscle stiffness due to other common myotonic disorders due to hereditary mutations of sodium channel, chloride channel, and other genes related to muscle function.

A whole limb that is stiff from multiple involuntary muscle contractions could be due to something as common as spasticity due to upper motor neuron damage. Of course, any case of corticospinal tract damage can result in spasticity. However, in the context of neuromuscular disorders, motor neuron disease is the primary consideration for spasticity due to upper motor neuron damage. If both upper and lower motor neuron findings are present, the diagnosis is generally amyotrophic lateral sclerosis. In this case, there is almost always distal asymmetric weakness which would be recognized as an NP5 pattern. If there is only spasticity and other upper motor neuron findings in a case of presumed motor neuron

disease, then the diagnosis is primary lateral sclerosis. Whole-muscle involuntary contractions can rarely be due to stiff person syndrome due to antibodies directed against glutamic acid decarboxylase on neurons. Stiff person syndrome most often involves all four extremities but at times can be two or three limbs.
In this discussion, we are not considering rigidity and excessive movements due to extrapyramidal disorders.

Bonus/ Exception Concept:
The Non-Length Dependent Sensory Neuropathy. (Figure 17)

Figure 17



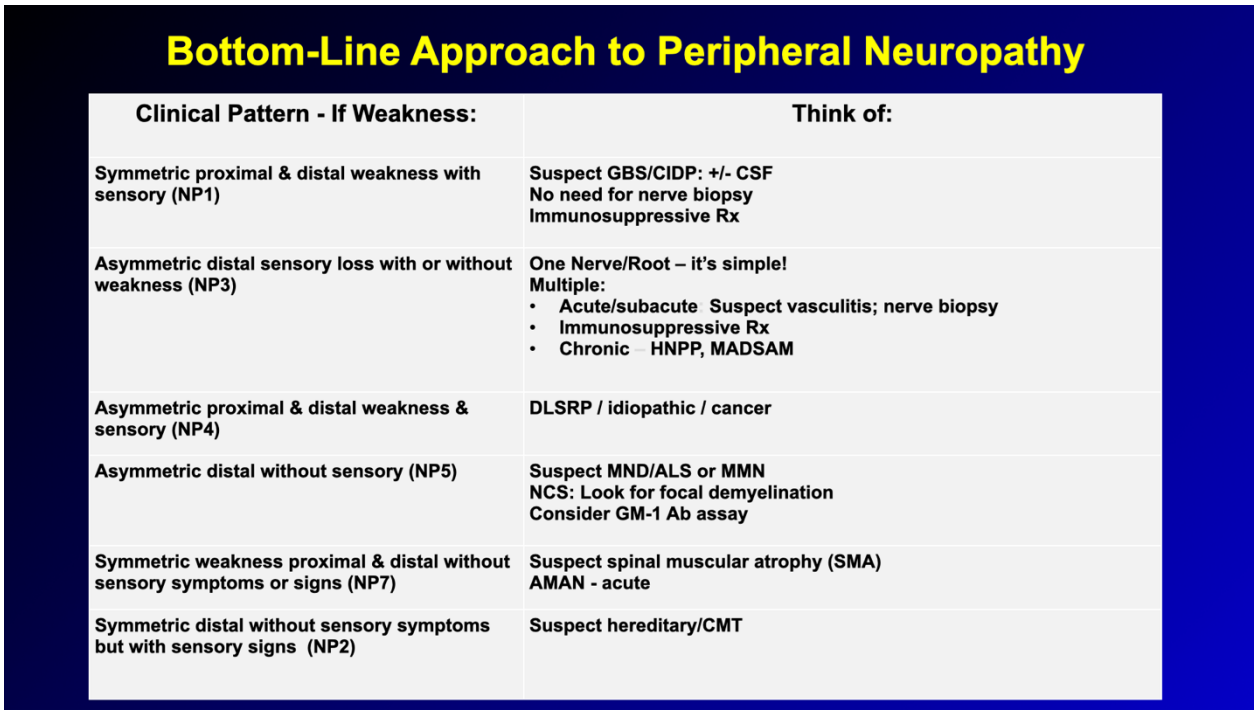
An exception to isolated sensory involvement being predominantly distal is the isolated sensory neuropathy that is non-length dependent. This was first described by Dr. Robert Wartenberg, and he even wrote a book on this entity (see Figure 18). Therefore, in the older literature, this has been referred to as Wartenberg's Sensory Neuritis. These patients have odd patches of numbness, tingling, and pain anywhere on their body including the trunk and face. The distribution can be proximal, distal, or proximal and distal and can be symmetric or asymmetric therefore if the sensory loss is both proximal, distal, and symmetric it would probably fit into the NP-1 pattern but there would be no weakness; if distal and symmetric- NP-2; if distal and asymmetric- NP-3; if proximal, distal, and asymmetric- NP-4; if only midline face or trunk- NP-8. Often these patients are thought to be psychogenic, but we now know that this can be a true non-length-dependent sensory neuropathy. Many of these cases only involve small fibers and electrodiagnostic studies would be normal. In these small fiber cases, a skin biopsy to assess epidermal nerve fiber loss is often needed to make the diagnosis. Some of these patients reportedly respond to intravenous immune globulin therapy. It is important that the clinician be aware of this sensory pattern and not immediately dismiss the patient as being psychogenic without further workup.

Some of the cases that Dr. Wartenberg described involved multiple distal sensory nerves and would fit the pattern of a sensory mononeuritis multiplex- NP-3. Another neuropathy that could be put in this pattern are the truncal diabetic sensory radiculopathies which can produce odd and asymmetric areas of sensory loss on the thorax and abdomen sometimes these cases are associated with the classic diabetic radiculopathy involving the lower and occasionally upper extremities described in the NP-4 pattern but sometimes they can occur in isolation without the extremity involvement.

Summary

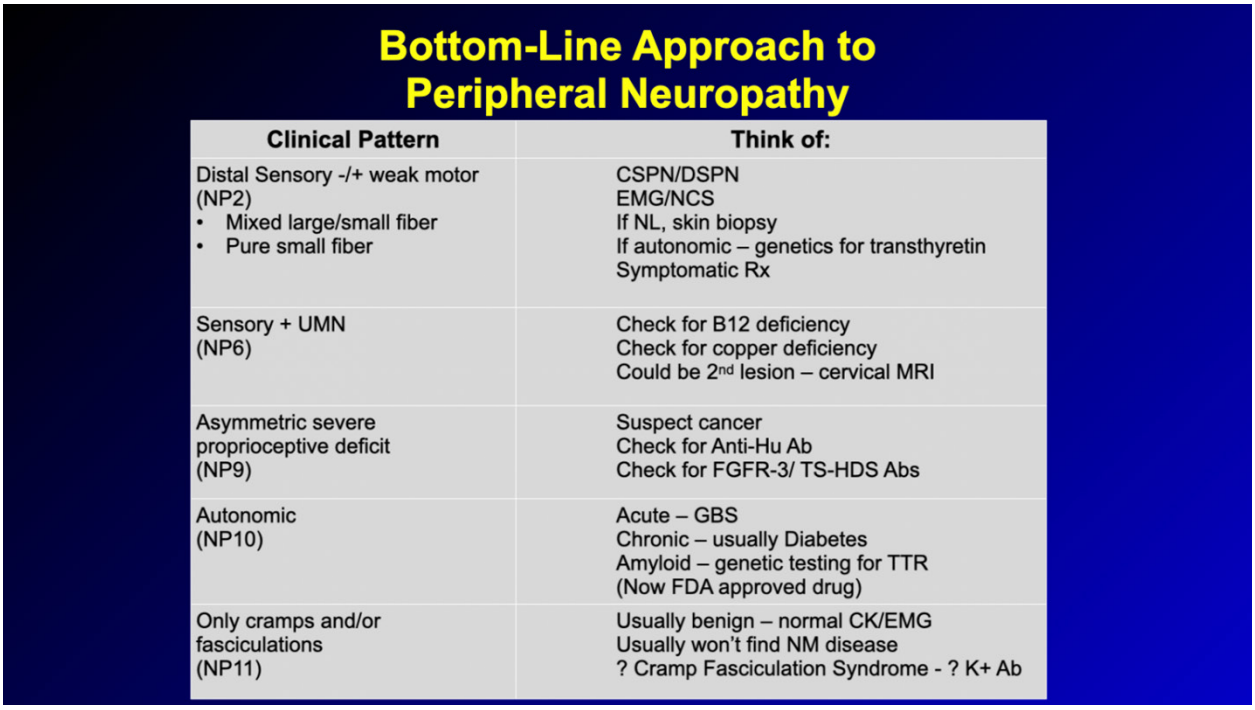
The following two figures summarize the patterns. Figure 18 involves patterns with motor involvement and Figure 19 involves patterns with predominant or exclusive sensory involvement.

Figure 18



If the pattern is symmetrical, proximal, and distal weakness with sensory loss then it is NP1- GBS or CIDP pattern. If it is asymmetric, distal weakness, and sensory loss and only one nerve or root are involved it is probably a simple mononeuropathy or radiculopathy. If multiple nerves or roots are involved, then it is mononeuropathy multiplex. If the pattern is asymmetric proximal and distal weakness with sensory loss, then it is most likely DLSRP until proven otherwise. If the pattern is asymmetric distal weakness without sensory loss, then this is the ALS/MMN pattern. The majority of these patients usually have motor neuron disease. If the pattern is symmetric weakness that is proximal and distal without sensory symptoms or signs, then this is most likely SMA which is now treatable. This is also the AMAN pattern when it is acute, a pure motor GBS variant. When the patient presents with distal weakness but without sensory signs, this is the dissociated sensory pattern and is likely to be a hereditary neuropathy.

Figure 19



If the neuropathic presentation is predominantly sensory, symmetrical, and distal this is the NP2 pattern (Figure 19). In the NP2 pattern, there may be mixed large or small fiber involvement, and the diagnosis is usually CSPN, DSPN, or the neuropathy associated with the metabolic syndrome, but isolated small fiber involvement can occur. If it is the same pattern but with upper motor neuron signs, then check for B12 and copper as this could be a myeloneuropathy- NP6. But the NP6 pattern can also imply that there could be an NP2 neuropathy with a second lesion such as a cervical spinal cord lesion or bihemispheric strokes. If it is an asymmetric severe proprioceptive deficit, NP9, suspect cancer but there are other causes as well. If there is autonomic involvement (NP10) and it is acute, consider GBS and if it is chronic, consider diabetes and familial amyloidosis. If the patient presents with only cramps or fasciculations it is most likely benign (NP11).

In Figure 20 we summarize all eleven clinical patterns of neuropathic disorders.

Summary of Eleven Clinical Neuropathic Patterns

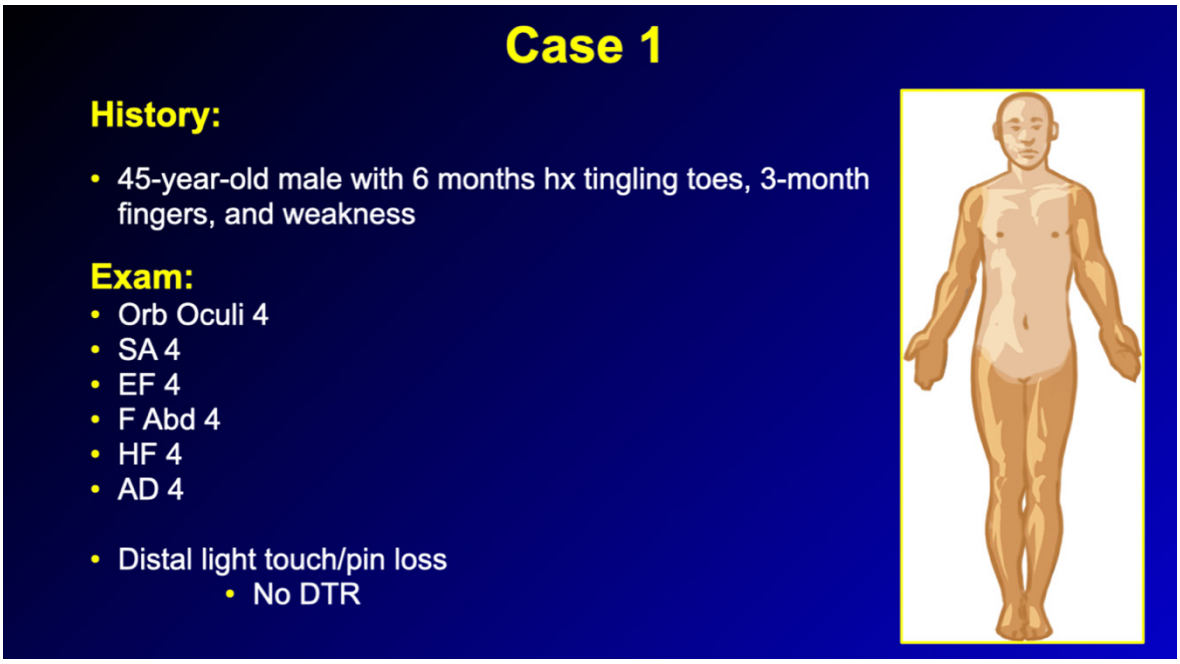
Figure 20

PATTERN	Proximal	Distal	Asymmetrical	Symmetrical	Sensory Symptoms	Severe Proprioceptive Loss	UMN Signs	Autonomic Symptoms/ Signs	Diagnosis
NP1-Symmetric, proximal, distal weakness w/ sensory loss	+	+		+	+				GBS / CIDP
NP2-Distal sensory loss w/without weakness		+		+	+				CSPN, metabolic, diabetes, drugs, hereditary, DADS
NP3-Asymmetric distal weakness w/ sensory loss		+	+		+				Multiple-vasculitis, HNPP, MADSAM, infection Single-Mononeuropathy, radiculopathy
NP4-Asymmetric proximal, distal weakness w/ sensory loss	+	+	+		+				Polyradiculopathy, plexopathy, DLSRP, cancer, idiopathic, infection
NP5-Asymmetric distal weakness w/ out sensory loss		+	+				+/-		+UMN-ALS/PLS -UMN-MMN
NP6-Symmetric sensory loss & upper motor neuron signs		+			+	+	+		B12 / copper deficiency; Friedreich's, ALD
NP7-Symmetric weakness w/out sensory loss*	+/-	+			+				Prox & Distal-SMA Distal-Hereditary motor neuropathy
NP8-Focal midline weakness*	+ Neck/trunk extensor +Bulbar +Diaphragm +CN 3,4,5,6,7			+ +			+ +		ALS ALS/ PLS CBS Isolated CN 3,4,5,6, 7-benign Multiple CN 3,4,5,6,7-underlying disease
NP9-Asymmetric proprioceptive loss w/out weakness			+		+	+			Sensory neuronopathy (ganglionopathy) CISP
NP10-Autonomic dysfunction								+	Diabetes, GBS, amyloid prophyria
NP11-Excessive muscle activity	+	+	+	+					Fasciculations, myokymia, neuromyotonia, stiff-person syndrome

CASE EXAMPLES
The following case studies demonstrate four of these patterns.

Case #1: 45-year-old male with 6 months of tingling in the toes, and 3 months in the fingers and he tells you he is weak. (Figure 21)

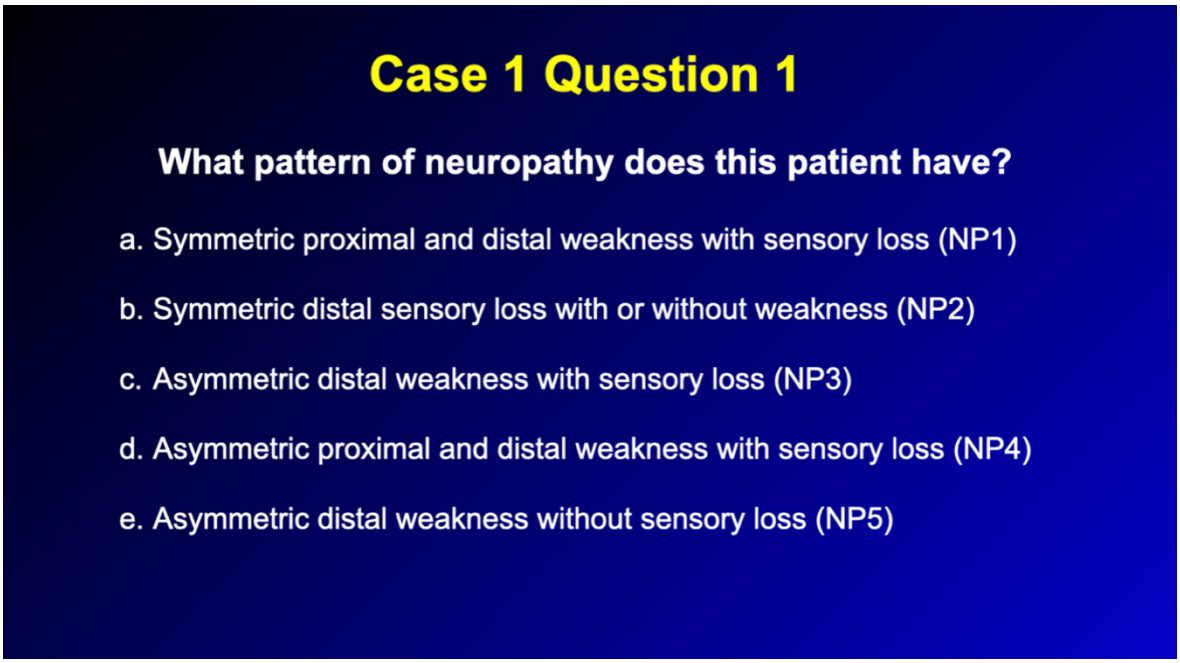
Figure 21



When you examine him, he has grade 4 weakness proximally and distally: orbicularis oculi, shoulder abduction, elbow flexion, finger abduction, hip flexion, and ankle dorsiflexion. There is a distal light touch and pinprick loss, and he has no reflexes.

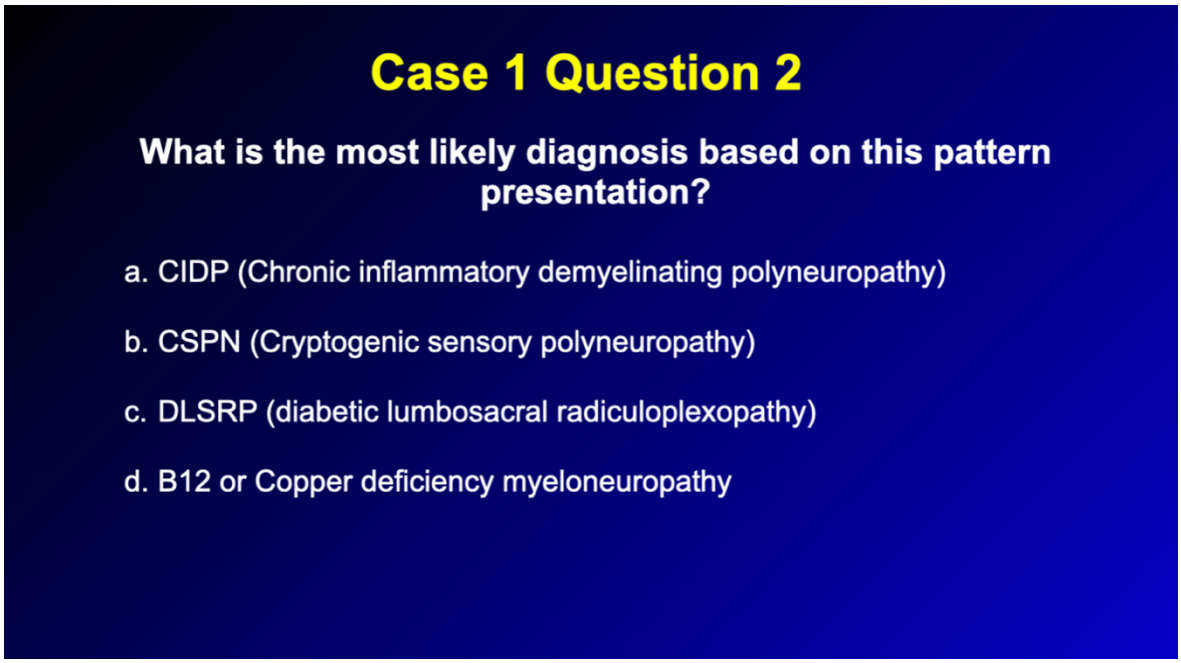
What pattern of neuropathy does this patient have? (Figure 22)

Figure 22



Answer: Symmetric proximal and distal weakness with sensory loss.
What is the most likely diagnosis based on this pattern? (Figure 23)

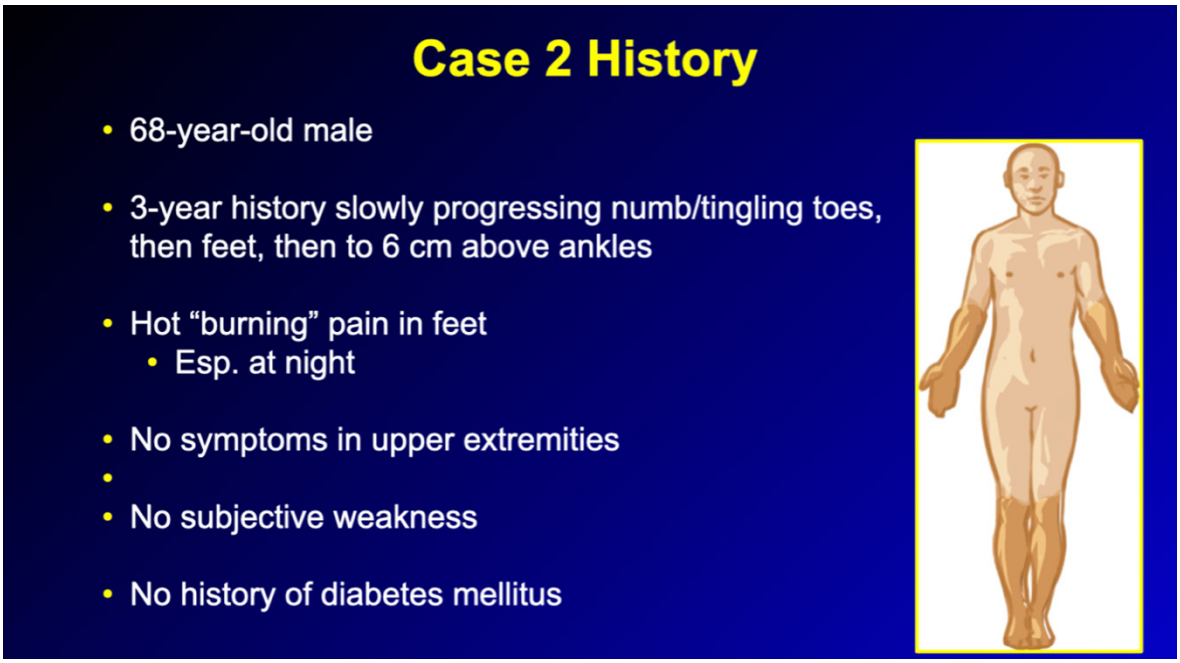
Figure 23



Answer: CIDP or Chronic inflammatory demyelinating polyradiculoneuropathy.

Case #2: 68-year-old male with a 3-year history of slowly progressive numbness and tingling of the toes that then progressed to the feet and eventually progressed to approximately 6 cm above the ankles. This occurred over 5 years. (Figure 24)

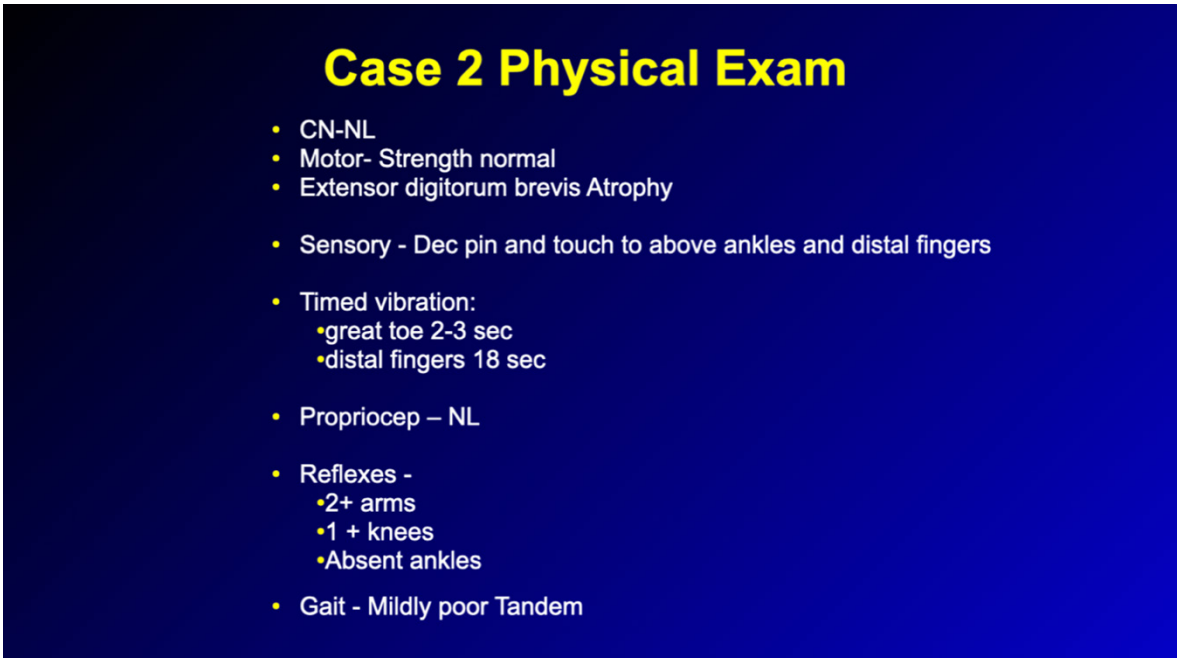
Figure 24



There is no hand involvement. The pain is a hot and burning sensation in the feet, especially at night. There is no subjective weakness and no history of diabetes.

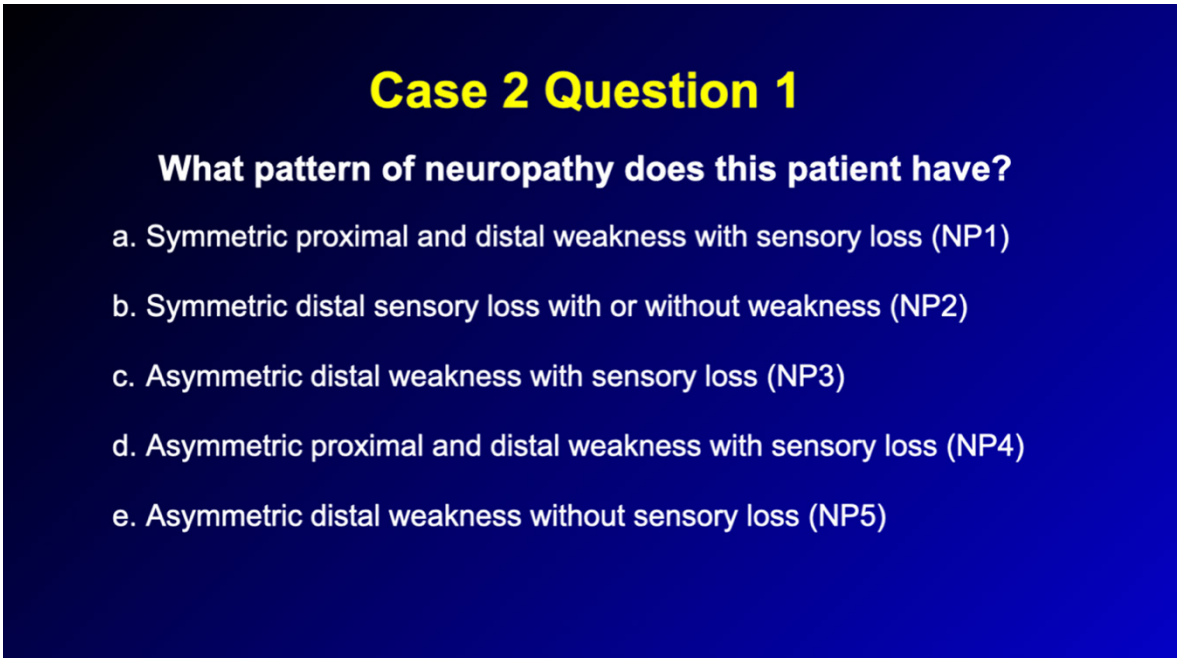
On exam (Figure 25), the cranial nerves are normal. The motor exam has normal strength although there is some extensor digitorum brevis atrophy in the feet. On sensory exam, there is decreased pinprick and touch above the ankles and also a slight decrease in the perception of these modalities in the fingertips. Timed vibration testing of the great toes is 2-3 seconds which is probably abnormal for his age. Proprioception is normal. Reflexes are 2 at the arms, 1 at the knees, and absent at the ankles. His routine gait is normal but when he tries to tandem walk he is unsteady.

Figure 25



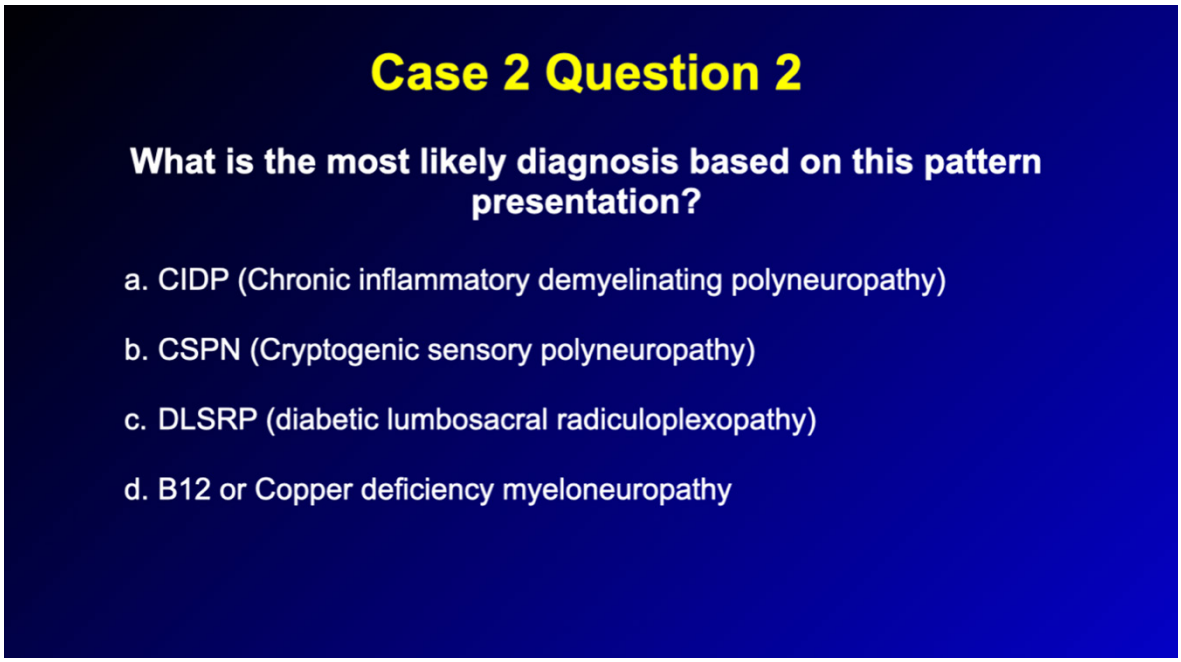
What pattern of neuropathy does this patient have? (Figure 26)

Figure 26



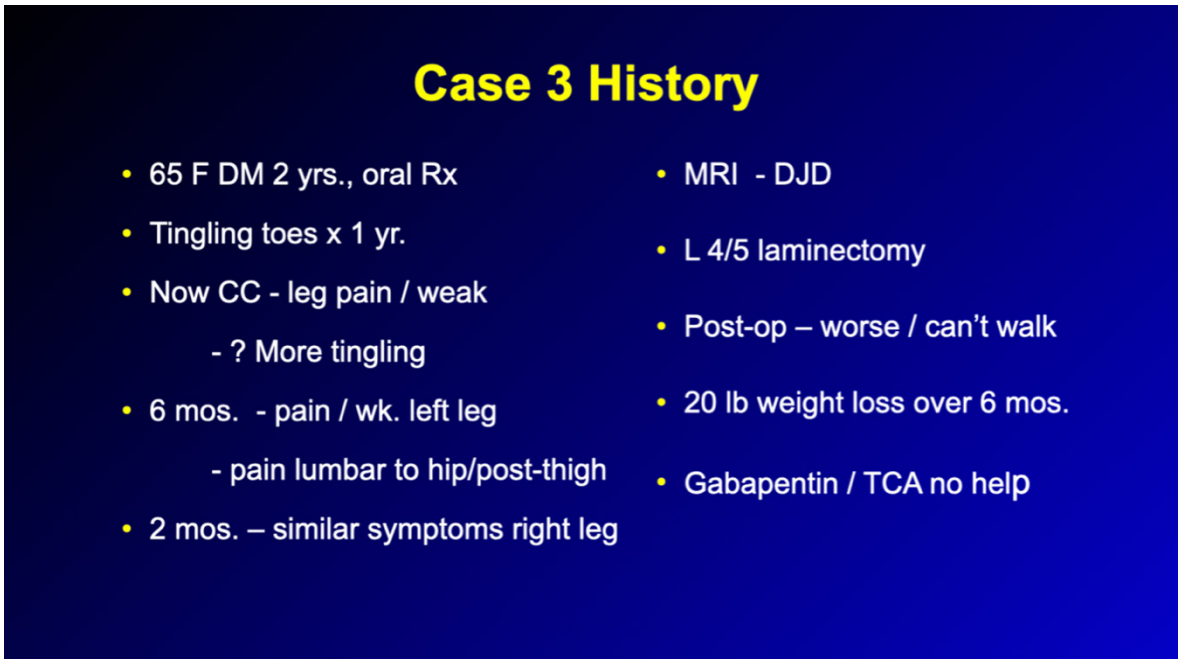
Answer: Symmetric distal sensory loss with or without weakness, NP2

What is the most likely diagnosis based on this pattern? (Figure 27)
Figure 27



Answer: Cryptogenic sensory polyneuropathy or CSPN.

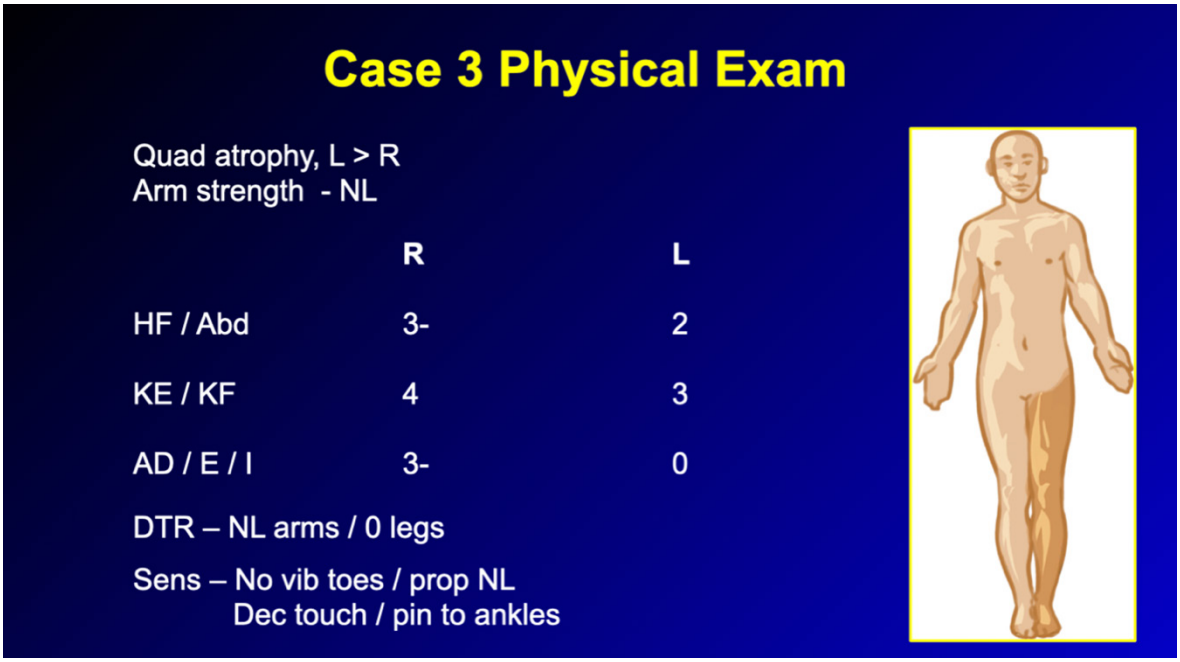
Case #3: 65-year-old diabetic female. She has been diabetic for 2 years and is on oral hypoglycemics. (Figure 28)
Figure 28



For the last year, she has had some tingling in the toes. For 6 months she has had leg pain and weakness, and it began 6 months ago in the left leg with severe back pain radiating in the hip and posterior thigh in the leg became weak and 2 months ago similar symptoms occurred in the right leg. This led her to a surgeon who did an MRI, and she then had an L4-L5 laminectomy. Post-operatively she continued to worsen. By the time a neurologist was consulted, she could not walk. The neurologist obtained the history that there was a 20lb weight loss over 6 months. She has been on gabapentin and tricyclic antidepressants for pain without help.

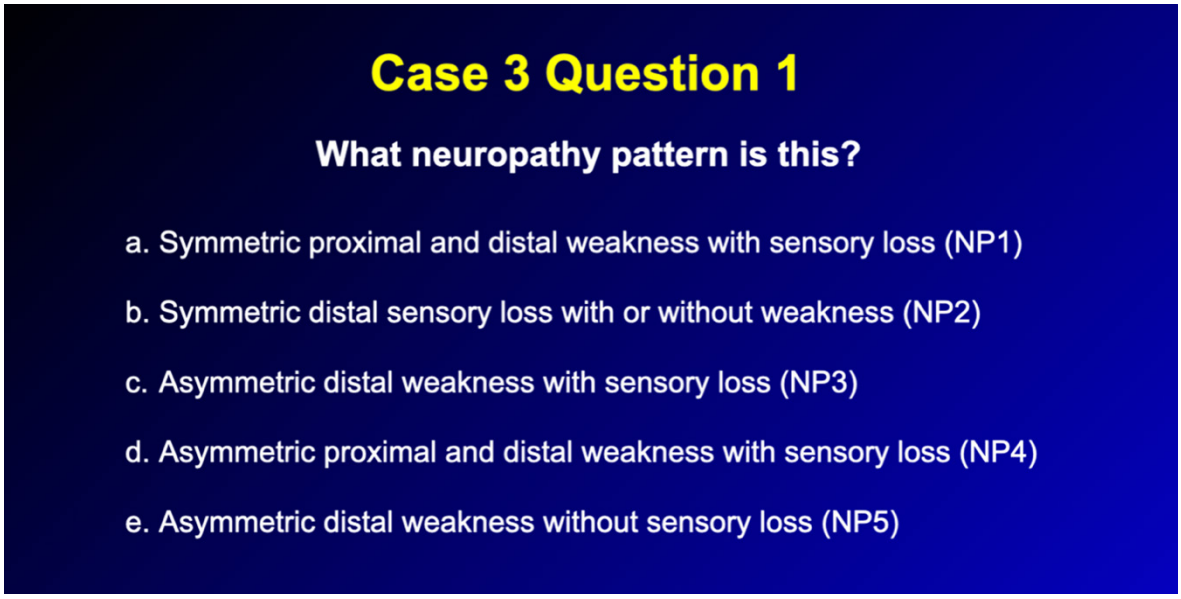
On examination, (Figure 29) there is severe quadriceps atrophy, worse on the left. Arm strength is completely normal. In the lower extremities, hip flexors and hip abductors are 3- on the right and 2 on the left; knee extensors and flexors are 4 on the right and 3 on the left; and ankle dorsiflexors and evertors and inverters are 3- on the right and zero on the left. Reflexes in the arms are normal but there are no reflexes at the knees or ankles. There is no vibration at the toes; proprioception is normal, and there is decreased pin and touch to the ankles.

Figure 29



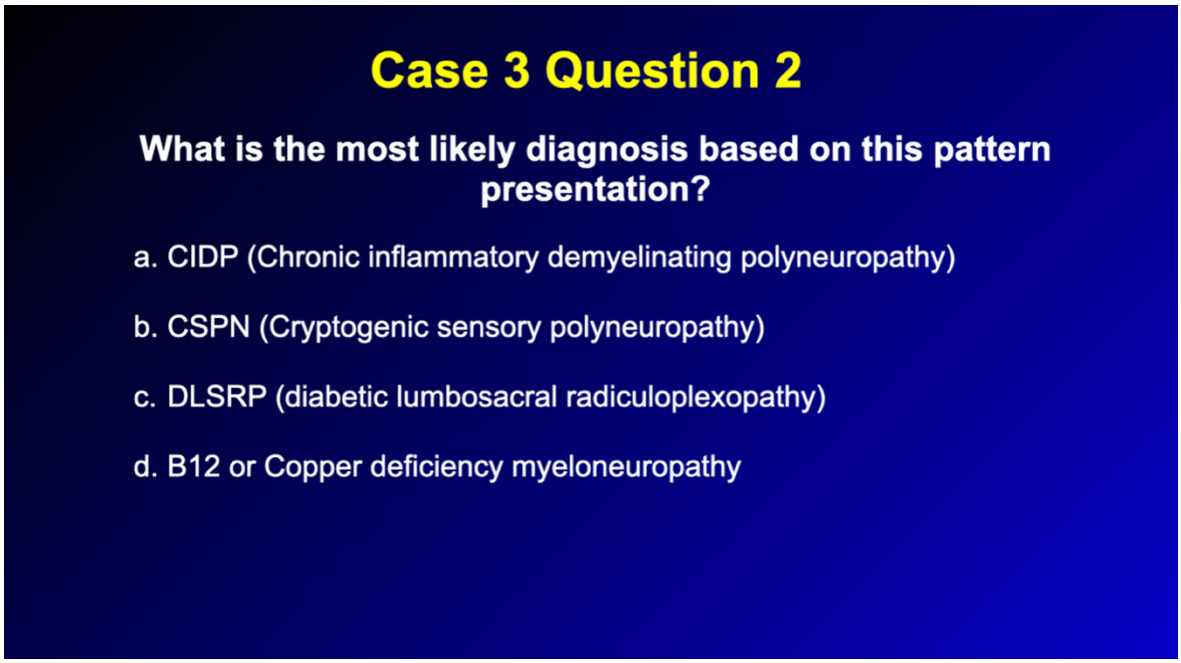
What neuropathy pattern is this? (Figure 30)

Figure 30



Answer: Asymmetric proximal and distal weakness with sensory loss
What is the most likely diagnosis based on this pattern? (Figure 31)

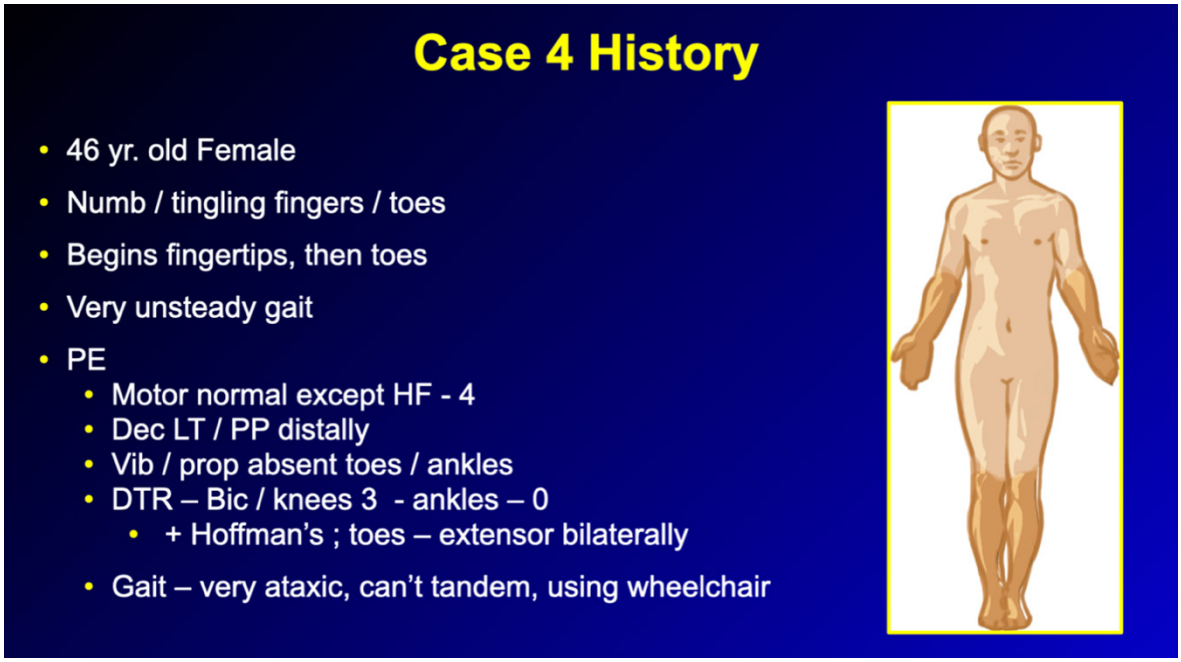
Figure 31



Answer: Diabetic lumbosacral radiculoplexopathy

Case #4: 46-year-old female with numbness and tingling in the fingers and toes. (Figure 32)

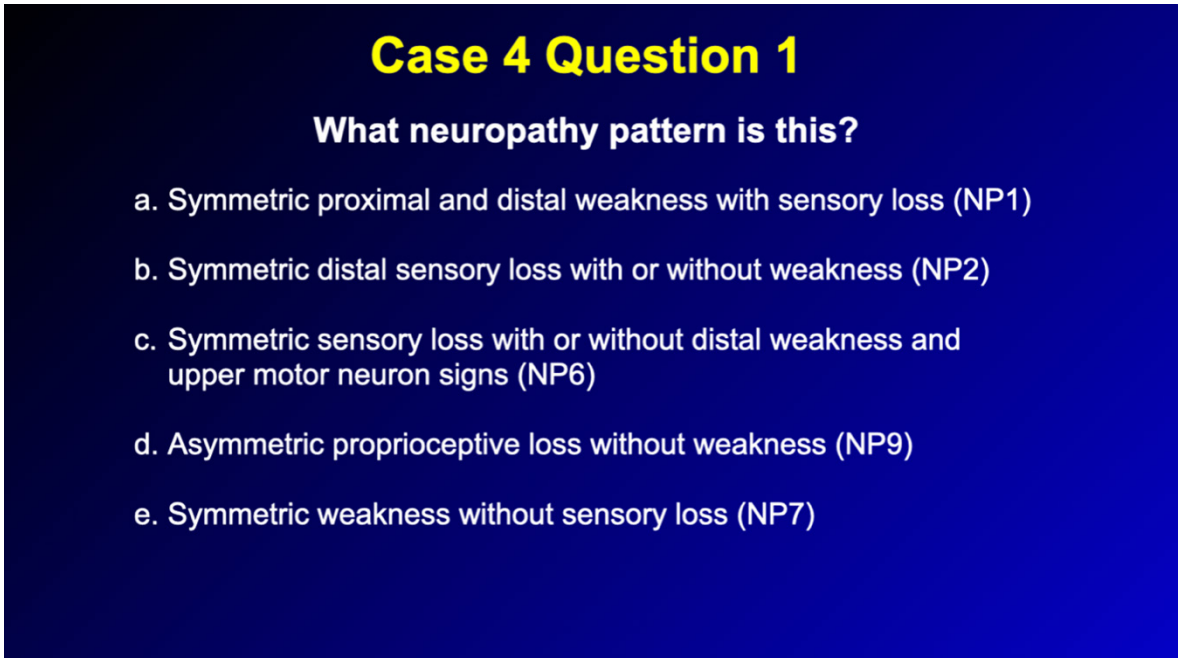
Figure 32



It began in the fingertips then went into the toes and has been gradually worsening over the last year and a half. She complains of a very unsteady gait. On examination, her motor strength is normal except for hip flexors that are grade 4. She has decreased light touch and pinprick distally, but her vibration and proprioception are absent at the toes and ankles. The reflexes are 3 at the biceps and knees and absent at the ankles. She has a positive Hoffman's reflex bilaterally and plantar responses are extensor bilaterally. Her gait is very ataxic, and she cannot tandem walk. She comes to the office in a wheelchair.

What neuropathy pattern is this? (Figure 33)

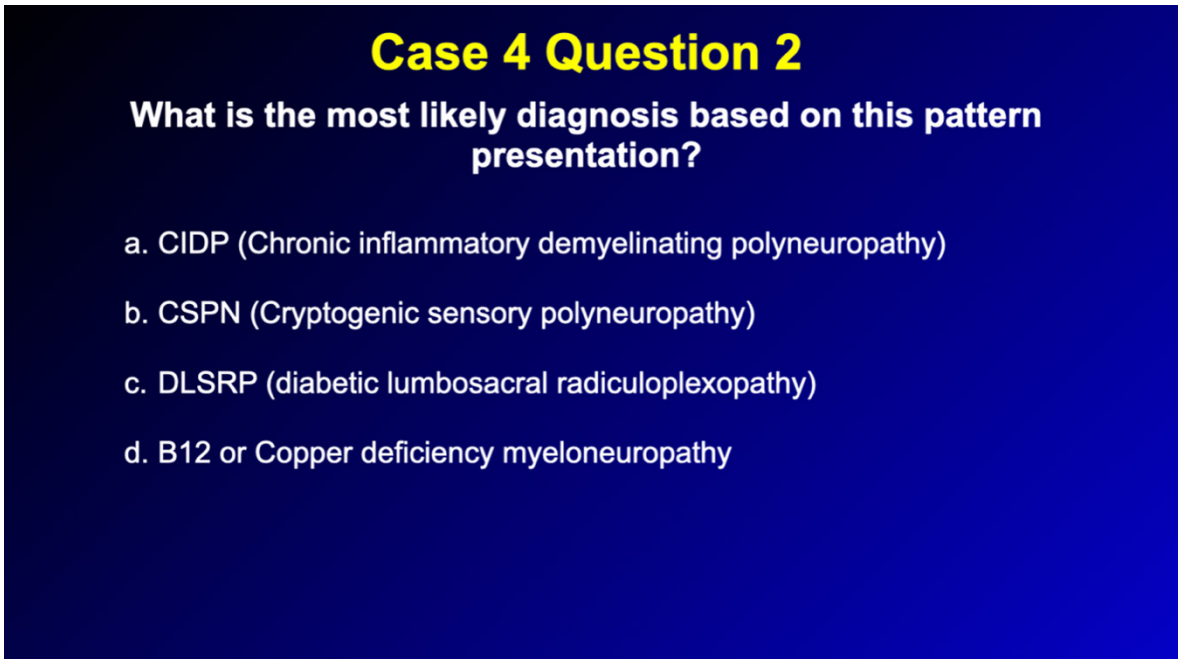
Figure 33



Answer: Symmetric sensory loss with or without distal weakness and upper motor neuron signs or NP6

What is the most likely diagnosis? (Figure 34)

Figure 34



Answer: B12 or copper deficiency myeloneuropathy

Conclusion

We end this review by showing a quote by William James who said, "The rivalry of the patterns is the history of the world" (Figure 35). We have paraphrased William James in the following ways:

The recognition of the patterns is the key to understanding neuromuscular disease

And

The patterns are like the operating systems for how we are supposed to think about neuromuscular disease (Figure 36).

Figure 35

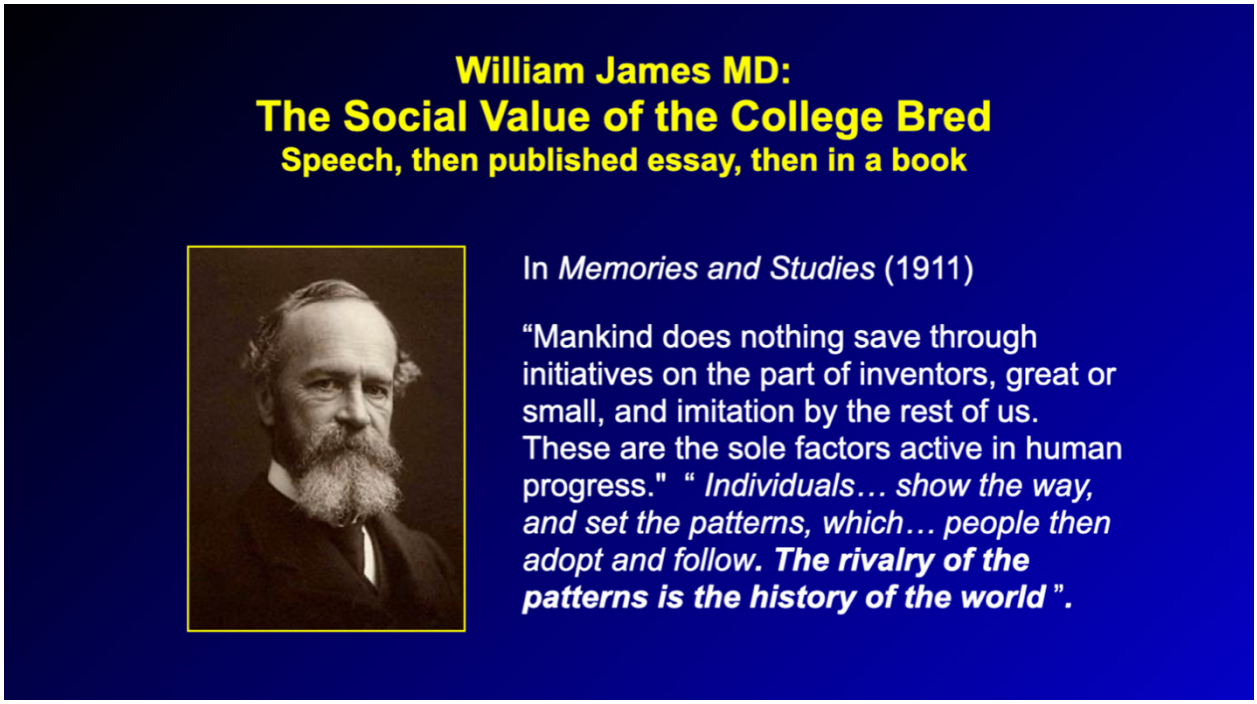


Figure 36

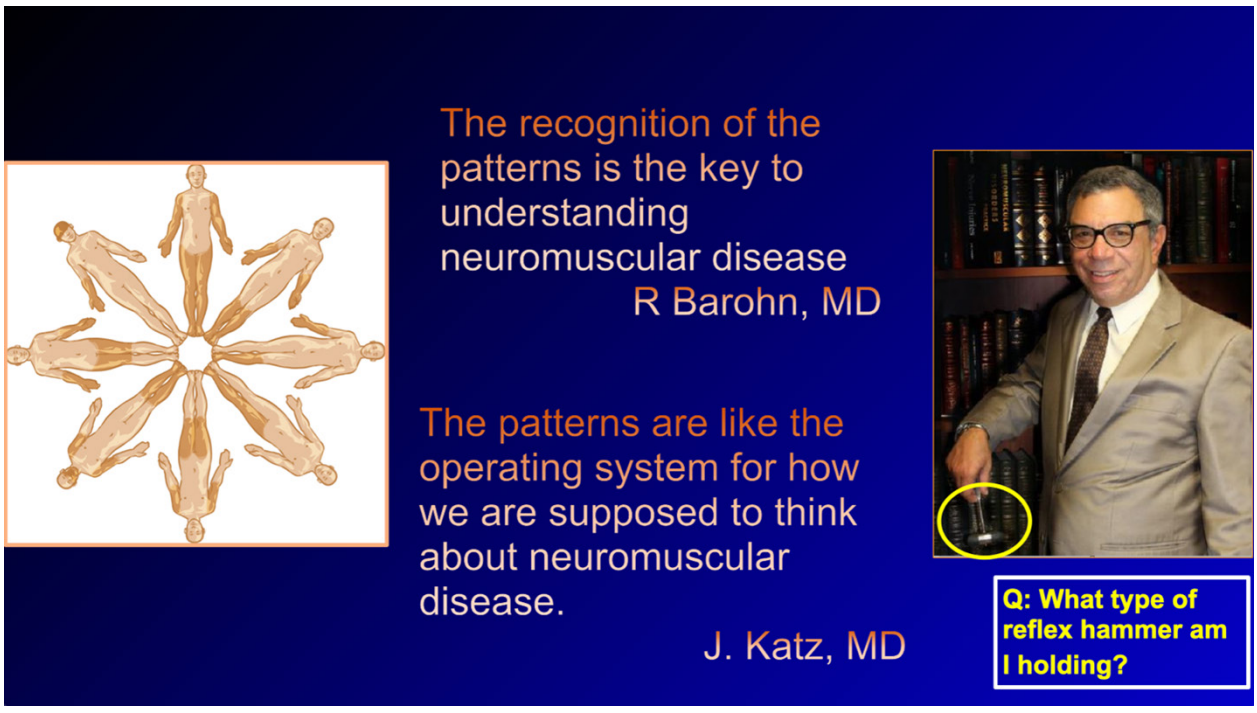


Figure 37

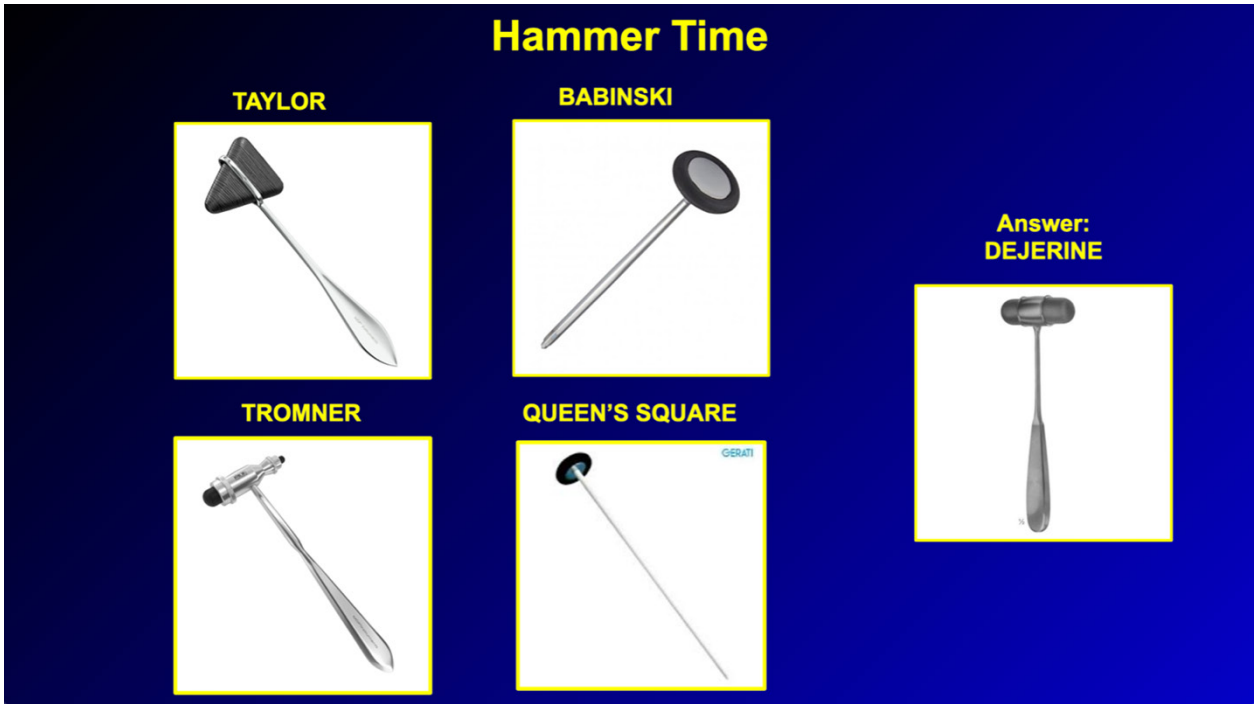


Figure 38

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