What Is (and Isn't) Neuropathy

Approach to Neuropathy

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Disclosure

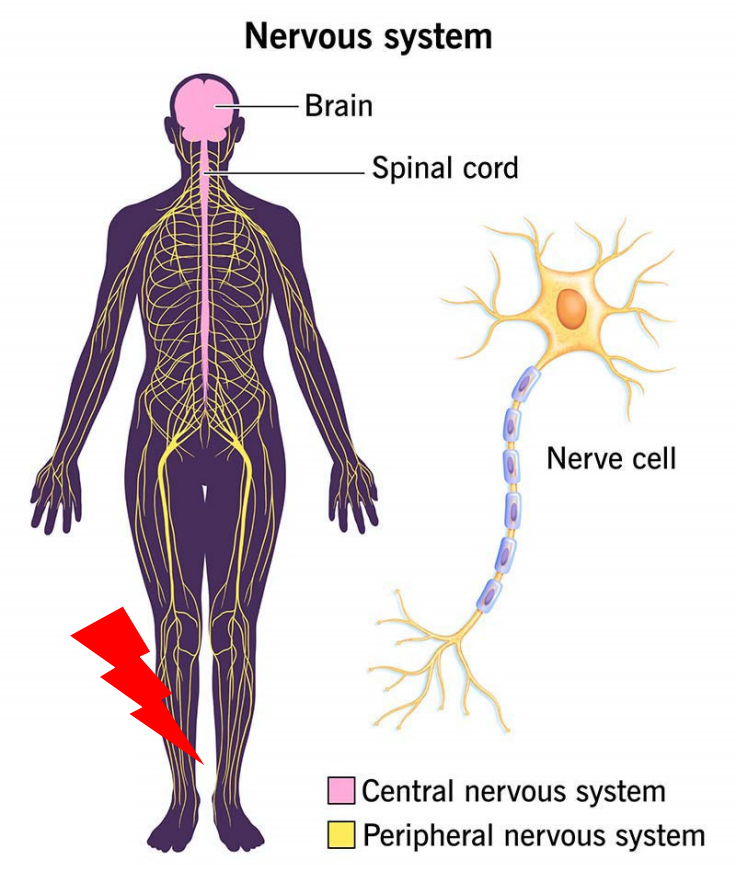
I have no conflict of interest in relation to this presentation.

Objectives

Upon completion of this activity, participants will be able to:

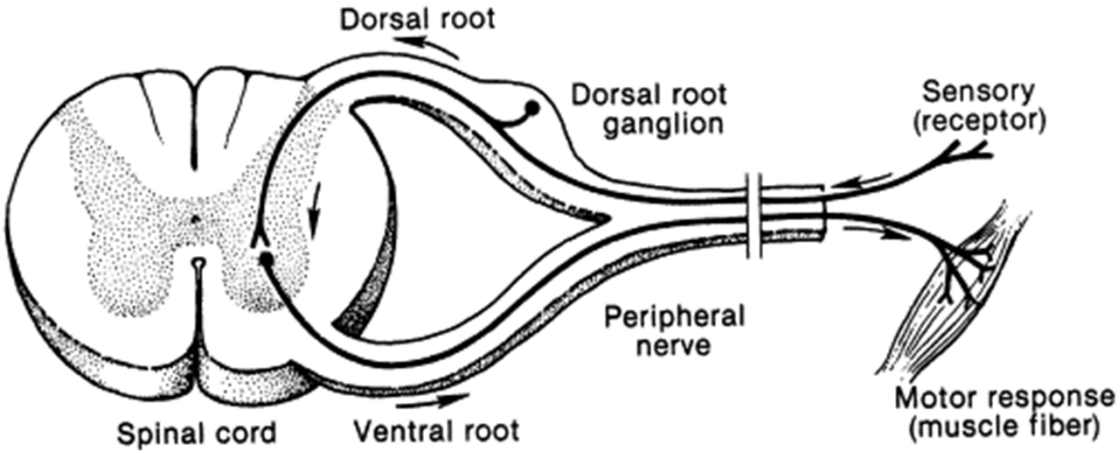
- *Discuss the importance of pattern recognition in diagnosing neuropathic disorders.*
- *Identify red flags that warrant referral to neurology.*
- *Describe the typical clinical presentation of diabetes-related neuropathy.*

Central versus Peripheral Nervous System



Upper motor neuron lesion	Lower motor neuron lesion
Lesion in the central nervous system which is above the anterior horn of the afferent pathways or above the motor nuclei of the efferent pathways.	Lesion in the peripheral nervous system
Reflexes: • Pathological reflexes such as positive Babinski and Hoffman's sign present. • Hyperreflexia or increased deep tendon reflexes present.	**Reflexes:** Hyporeflexia or diminished reflexes present.
Strength: Hypertonia and spasticity.	**Strength:** Hypotonia, atrophy, reduced strength, flaccidity. Atrophy in distribution of peripheral nerve.
Sensation: Sensory deficits will be dependent on which part of the sensory tracts are impacted by the lesion. **Dorsal column medial lemniscus** pathway is responsible for our discriminatory sense: • Two-point discrimination • Vibration sense • Proprioception • Light touch **Spinothalamic tract** is responsible for our self-protective reactions in response to stimuli that are potentially harmful: • Nociceptive information (pain) • Temperature • Tickle, itch and sexual sensations • Crude touch (ability to identify the sensation of touch without localisation)	**Sensation:** Sensory deficits will be dependent on the spinal nerve involved - creating a **dermatomal loss of sensation** *or* the **cutaneous nerve** involved, which would impact a patch of skin on the limb.

What is Neuropathy



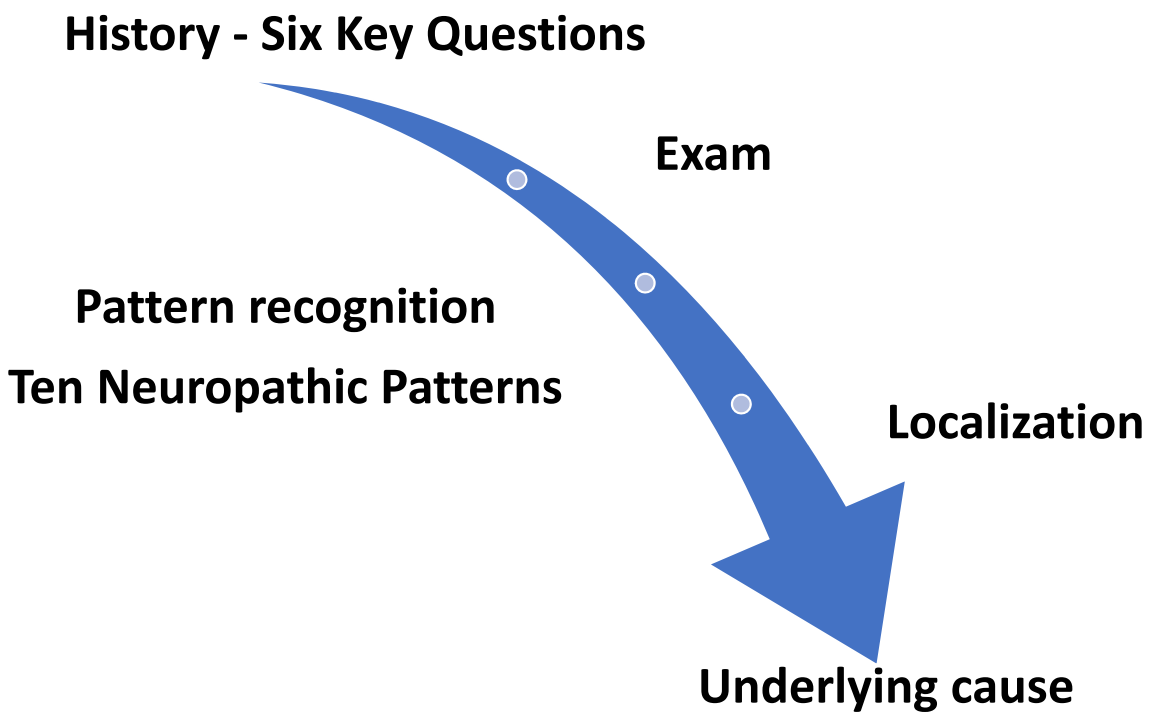
? Neuropathic disorders

- *Sensory neuron/sensory ganglion*
- *Motor neuron/anterior horn cell*
- *Nerve root*
- *Plexus*
- *Peripheral nerve*
  - *Large versus small fiber nerve*

Small and large fiber peripheral nerves

		Large Fiber Neuropathy	Small Fiber Neuropathy
Symptoms		• Negative sensory symptoms • +/- motor symptoms	• Positive sensory symptoms • No motor symptoms
Exam	**Motor**	Maybe impaired	Normal
	Reflexes	Reduced	Normal
	Sensory	Loss of vibratory and proprioceptive sensations	Loss of temperature and pinprick sensations
NCS/EMG		Abnormal	Normal

Approach to Neuropathic Disorders



Approach to Neuropathic Disorders: Six Key Questions

1. What systems are involved?

Motor, sensory, autonomic, or combinations

2. What is the distribution of weakness?

- Distal, proximal, or proximal and distal
- Focal, asymmetric or symmetric

3. What is the nature of the sensory involvement?

- Positive or negative symptoms
- Distal, proximal, or proximal and distal
- Focal, asymmetric or symmetric

4. What is the temporal evolution?

- Acute (days to 4 weeks)
- Subacute (4 to 8 weeks)
- Chronic (> 8 weeks)
- Preceding events, drugs, toxins

5. Is there evidence for a hereditary neuropathy?

- Family history
- Skeletal deformities
- Lack of sensory symptoms despite sensory signs

6. Is there upper motor neuron involvement?

Barohn RJ, Amato AA. Neurol Clin. 2013 May;31(2):343-61.

Approach to Neuropathic Disorders: Ten Patterns

1. Symmetric distal sensory loss with or without distal weakness - distal symmetric polyneuropathy
2. Symmetric proximal and distal weakness with sensory loss - inflammatory radiculoneuropathy
3. Symmetric sensory loss with upper motor neuron findings - myeloneuropathy
4. Asymmetric proprioceptive sensory loss without weakness - sensory neuronopathy
5. Asymmetric distal weakness without sensory loss - motor neuronopathy or motor neuropathy
6. Autonomic Symptoms and Signs
7. Asymmetric distal weakness with sensory loss
8. Asymmetric proximal and distal weakness with sensory loss

} Asymmetric weakness with sensory loss

9. Symmetric weakness without sensory loss*
10. Focal midline proximal symmetric weakness*

* Overlaps with myopathies and NMJ disorders

Barohn RJ, Amato AA. Neurol Clin. 2013 May;31(2):343-61.

Pattern 1: Symmetric distal sensory loss with or without distal weakness - distal symmetric polyneuropathy

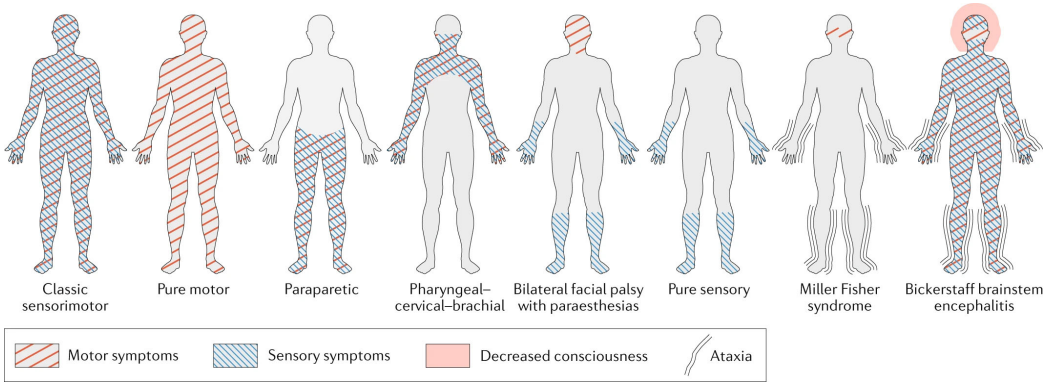
- Toxic and metabolic polyneuropathy (sensory > motor)
- Hereditary neuropathy (motor > sensory)

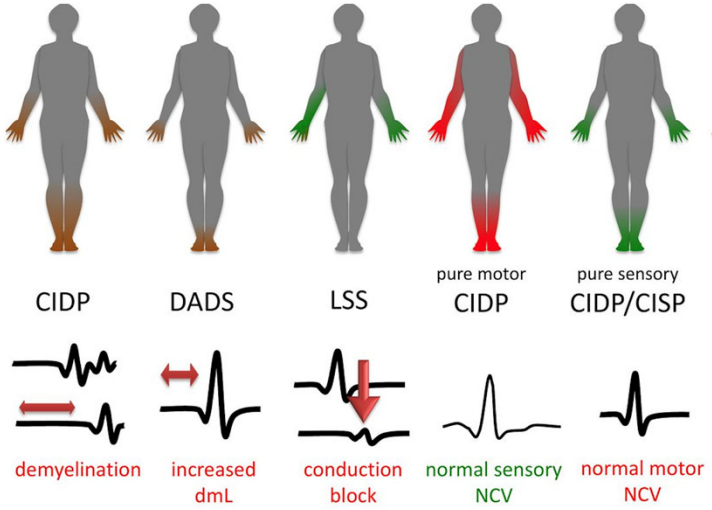
Pattern 1: Symmetric distal sensory loss with or without distal weakness - distal symmetric polyneuropathy

1) Screening lab tests may be considered for all patients with polyneuropathy (Level C).
   - Tests that provide the highest yield of abnormality are blood glucose, serum B12 with metabolites (methylmalonic acid with or without homocysteine), and serum protein immunofixation electrophoresis (Level C).
   - If there is no definite evidence of diabetes by routine testing of blood glucose, testing for impaired glucose tolerance may be considered in distal symmetric sensory polyneuropathy (Level C).
2) Genetic testing should be conducted for the accurate diagnosis and classification of hereditary neuropathies (Level A). Genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype (Level C).

Pattern 2: Symmetric proximal and distal weakness with sensory loss - inflammatory radiculoneuropathy

- Inflammatory demyelinating polyradiculoneuropathy (GBS and CIDP)
- Classic GBS and CIDP phenotypes





GBS reaches disease nadir within 4 weeks and CIDP progresses beyond 8 weeks.

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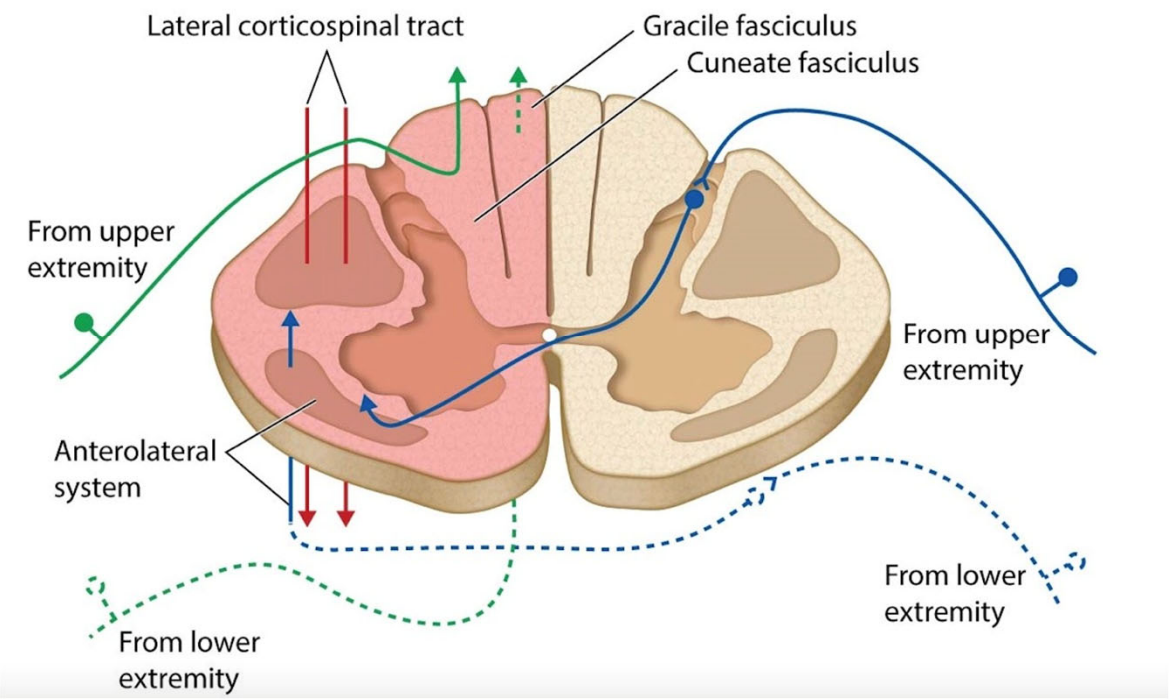
Leonhard SE, Mandarakas MR, et al. Nat Rev Neurol. 2019 Nov;15(11):671-683.
Lehmann HC, Burke D, et al. J Neurol Neurosurg Psychiatry. 2019 Sep;90(9):981-987

Pattern 3: Symmetric sensory loss with upper motor neuron findings - Myeloneuropathy

Myelopathic signs as well as signs of a polyneuropathy are found.

- B12 deficiency
- Copper deficiency
- Zinc toxicity
- Autoimmune disorders: Sarcoidosis, Sjogren syndrome, …
- Infections: HIV, HTLV, …
- Genetic disorders: adrenomyeloneuropathy, Friedreich's ataxia, …

Pattern 3: Symmetric sensory loss with upper motor neuron findings - Myeloneuropathy



Pitfall: when a posterior myelopathy looks like a neuropathy

Pattern 4: Asymmetric proprioceptive sensory loss without weakness

- Sensory neuronopathy (ganglionopathy)
- Chronic immune sensory polyradiculopathy (CISP)

Causes of Sensory Neuronopathy (Ganglionopathy)

Cancer (Paraneoplastic)
Sjögren's syndrome
Idiopathic sensory neuronopathy
Cisplatinum and other analogues
Vitamin B6 toxicity
HIV-related sensory neuronopathy

Barohn RJ, Amato AA. Neurol Clin. 2013 May;31(2):343-61.

Pattern 5: Asymmetric distal weakness without sensory loss - motor neuronopathy or motor neuropathy

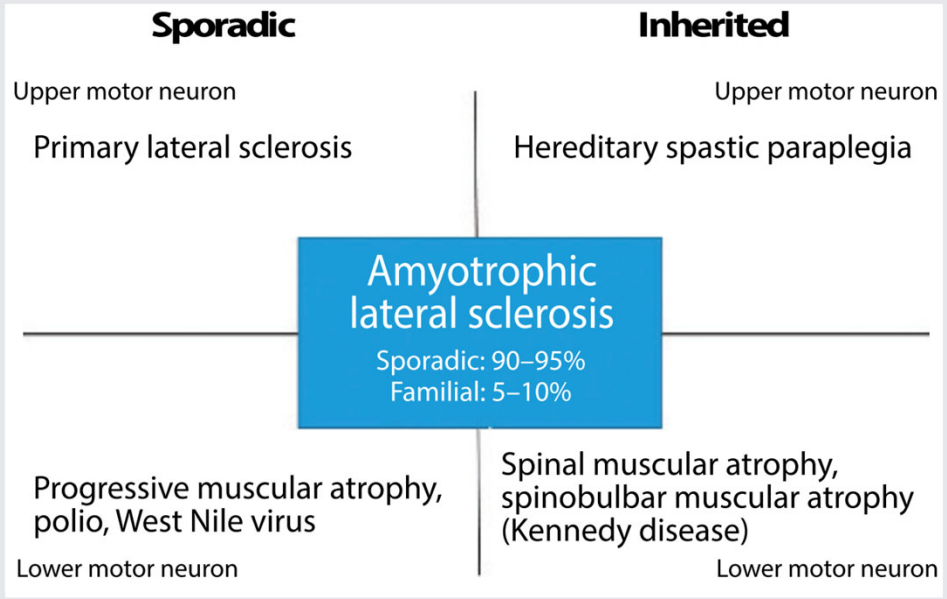


FIGURE 6-1 The spectrum of motor neuron diseases.

Motor Neuropathy:

- Multifocal motor neuropathy
- Lead poisoning

Pattern 6: Autonomic Symptoms and Signs

Peripheral Neuropathies With Autonomic Nervous System Involvement

Hereditary sensory autonomic neuropathy
Diabetes mellitus
Amyloidosis (familial and acquired)
Guillain-Barre syndrome
Vincristine induced
Porphyria
HIV-related autonomic neuropathy
Idiopathic pandysautonomia

Barohn RJ, Amato AA. Neurol Clin. 2013 May;31(2):343-61.

Pattern 7/8: Asymmetric weakness with sensory loss

- Multiple nerves - mononeuropathy multiplex
  - Vasculitis
  - Hereditary neuropathy with liability to pressure palsies (HNPP)
  - Multifocal CIDP
  - Infectious (leprosy, lyme, sarcoid, HIV)
- Radiculopathy
- Plexopathy

Pattern 9: Symmetric weakness without sensory loss

- Proximal and distal weakness
  - Spinal muscular atrophy
- Distal weakness
  - Hereditary motor neuropathy
- Also consider distal myopathy

Pattern 10: Focal midline proximal symmetric weakness

- Bulbar weakness - ALS, PLS
- Also consider myopathy and neuromuscular junctional disorders

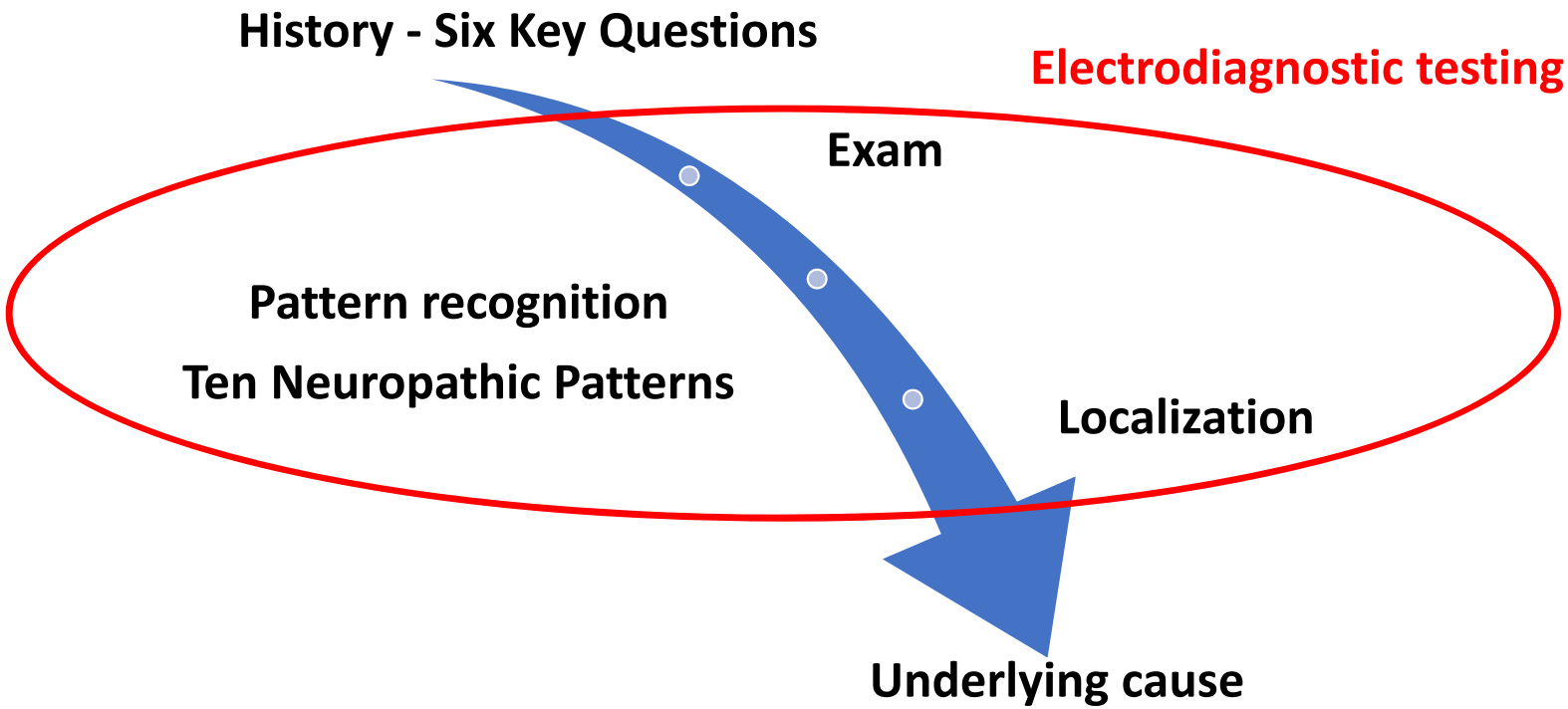
Role of Electrodiagnostic Testing (NCS/EMG)

Extension of clinical exam

- Help with localization
  - *In patients with weakness, is it myopathy, neuromuscular junctional disorder, motor nerve disorder, or a motor neuron disease?*
- Help with better characterization of lesions
  - *In polyneuropathy: length- versus non-length dependent, sensory versus motor versus sensorimotor, symmetric versus asymmetric, axonal loss versus demyelination*

- Does not specify disease etiology
- Normal in central nervous system disorders (needle EMG may show reduced activation)
- Normal in small fiber neuropathy

Approach to Neuropathic Disorders



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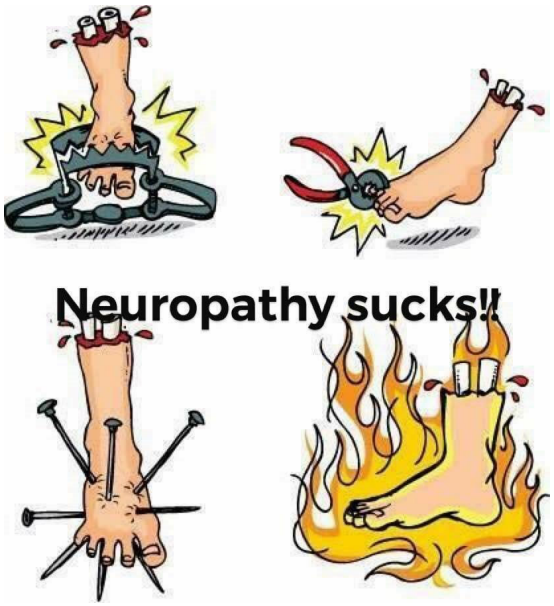
Red Flags that warrant a referral to neurology

Not chronic distal symmetric sensory>motor polyneuropathy

- **Subacute or acute onset, rapid progression**
- Proximal > distal involvement
- Asymmetry
- Motor > sensory
- Suspect localizations other than peripheral nerve, such as **motor neuron**, sensory neuron
- ? Autonomic involvement

Diabetes related neuropathy
5 different phenotypes



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Diabetes related neuropathy - Case 1

A 50-year-old woman with a 15-year history of type 2 diabetes was referred for sensory disturbances.

Her symptoms had begun almost a year ago as altered sensation in her toes, as if her socks were too tight, and had slowly ascended from her feet to her ankles and the back of her legs. Sometimes she had zaps of shooting pain in her feet, which kept her from sleeping. She often had to keep her feet uncovered because she found the blankets irritating.

On examination, she had normal strength, reflexes, and coordination. Sensory examination showed intact proprioception but reduced vibratory sensation at the great toes. She had decreased sensation to pinprick distally to just above the ankles. Her gait was normal.

Adapted from Elafros MA, Callaghan BC. Continuum (Minneap Minn). 2023 Oct 1;29(5):1401-1417.

Diabetes related neuropathy - DSPN

- Most common type of diabetic neuropathy.
- Symmetric, altered sensation in the toes that spreads up the calves before beginning in the fingers and hands in a stocking-glove pattern.
- Chronic onset, length-dependent, symmetric, large and small fiber involvement, sensory > motor involvement.

SPECIAL ARTICLE Level of Recommendation

Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary

Report of the AAN Guideline Subcommittee

Table 3 Efficacy of Oral Medications for Painful Diabetic Neuropathy by Class Effect

Medication class	SMD[a]	LCL	UCL	Number of articles	Number of patients	Conclusion	Confidence
Gabapentinoids	0.44	0.25	0.63	16	3,550	Probably more likely than placebo to improve pain	Moderate
Sodium channel blocker	0.56	0.25	0.87	5	566	Probably more likely than placebo to improve pain	Moderate
SNRI	0.47	0.34	0.60	9	1,884	Probably more likely than placebo to improve pain	Moderate
SNRI-opioid	0.62	0.38	0.86	4	775	Probably more likely than placebo to improve pain	Moderate
TCA	0.95	0.15	1.75	3	139	Possibly more likely than placebo to improve pain	Low

Abbreviations: LCL = lower confidence limit; SMD = standardized mean difference; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressants; UCL = upper confidence limit.
[a] SMD >0 indicates intervention is clinically better than placebo.

Table 1 Medication Dosage and Duration Information

Medication class	Medication	Dosage, mg/d	Duration, wk
SNRI	Duloxetine	40–60	12
SNRI	Venlafaxine	150–225	6
SNRI	Desvenlafaxine	200	13
Gabapentinoid	Gabapentin	900–3,600	4–8
Gabapentinoid	Pregabalin	300–600	5–12
Gabapentinoid	Mirogabalin	15–30	5
Sodium channel antagonist	Oxcarbazepine	1,400–1,800	16
Sodium channel antagonist	Lamotrigine	200–400	6
Sodium channel Antagonist	Lacosamide	400	12
Sodium channel blocker	Valproic acid	1,000–1,200 or 20 mg/kg/d	4–12
TCA	Amitriptyline	75–150	6
Capsaicin	Capsaicin	8% for 30 min/ application or 0.075% 4 times per day	12

Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

Diabetes related neuropathy - Case 2

A 60-year-old man presented to the emergency department after a syncopal episode. His evaluation after the episode was unremarkable.

Although this was the first time that he had lost consciousness, he noted that for the past few years, he had been increasingly “woozy” when getting out of bed to use the bathroom at night. In addition to long-standing diet-controlled type 2 diabetes, he was taking lisinopril for hypertension and atorvastatin for hyperlipidemia.

His neurologic examination was generally unremarkable except for decreased sensation to pinprick on his feet. His resting heart rate was 105 beats/min, and his blood pressure while lying down was 120/75 mm Hg and 90/50 mm Hg after standing for 3 minutes.

Adapted from Elafros MA, Callaghan BC. Continuum (Minneap Minn). 2023 Oct 1;29(5):1401-1417.

Diabetes related neuropathy - Dysautonomia

Signs of autonomic dysfunction:

- Cardiovascular autonomic neuropathy:
  - Early signs are from parasympathetic dysfunction of the vagal nerve → elevated resting heart rate and impaired heart rate variability.
  - Later in the course, decreased sympathetic activity → decreased peripheral vasoconstriction.
  - Combined parasympathetic and sympathetic autonomic nerve damage eventually leads to decreased cardiac output.
  - Dizziness, decreased exercise tolerance, orthostatic hypotension (defined as a drop in SBP of >20 mm Hg or DBP of >10 mm Hg when going from lying to sitting or sitting to standing after 3 minutes) and syncope.
- GI autonomic dysfunction: gastroparesis, constipation
- GU autonomic dysfunction: bladder dysfunction, sexual dysfunction.

Diabetes related neuropathy - Case 3

A 62-year-old man with history of type 2 diabetes (most recent A1c 7.5%) presents with severe pain in his right thigh and hip as well as weakness in the right leg.

The pain began about two months ago, described as sharp, burning, and radiating from the lower back into the anterior thigh. Over the past few weeks, he has noticed progressive weakness in his right leg and difficulty climbing stairs.

On further questioning, the patient reports significant unintentional weight loss (about 15 pounds) over the past three months, despite having a good appetite.

Lumbosacral Radiculoplexus Neuropathy (Diabetic Amyotrophy)

- Uncommon, with a prevalence of 2.79 cases per 100,000 people over 5 years in Olmsted County, Minnesota.
- Unlike other diabetic neuropathies, patients often have fairly well-controlled diabetes, with a median hemoglobin A1C of 7.5% in one study.
- Often occurs in the setting of weight loss, typically more than 4.5 kg (10 lb).
- Acute, severe pain in the hip or thigh described as burning, tightness, or allodynia. This is followed by lower limb weakness that is initially focal and then generalizes to the entire limb. Weakness can progress over months.
- Pain often improves first, depending on how long it takes to seek care, patients may only have asymmetric lower limb weakness and muscle atrophy at the time of evaluation.

Ng PS, Dyck PJ, et al. Neurology. 2019 Mar 12;92(11):e1188-e1194.
Dyck PJ, Norell JE, et al. Neurology. 1999 Dec 10;53(9):2113-21.

Lumbosacral Radiculoplexus Neuropathy (Diabetic Amyotrophy)

- Although microvascular inflammation likely plays a substantial role, limited data exist to support the use of immunotherapy in diabetic lumbosacral radiculoplexus neuropathy.
- There is one completed placebo-controlled trial (N = 75) using intravenous methylprednisolone in diabetic amyotrophy (Dyck 2006). The results have not been fully published and were not available for analysis.

Chan YC, Lo YL, et al. Cochrane Database Syst Rev. 2017 Jul 26;7(7):CD006521

Diabetes related neuropathy - Case 4

A 30-year-old man presented to the clinic for diffuse, shock like pain.

He had been diagnosed with type 1 diabetes as a teenager and historically had poor glycemic control. However, he noted that he recently got engaged and, for the past 3 months, had been seeking regular medical care to “turn over a new leaf.” Three weeks before this presentation, he had developed new burning and shock like pain in his hands, feet, and abdomen. He had no prior symptoms of neuropathy.

On examination, he had normal strength and reflexes. Vibration sensation and proprioception were also normal. He endorsed severe pain to pinprick in his hands and feet. Similarly, he endorsed pain across his abdomen that did not localize to one dermatome.

A review of his recent laboratory testing revealed that his hemoglobin A1C was historically between 14% and 16% but most recently was 9%.

Adapted from Elafros MA, Callaghan BC. Continuum (Minneap Minn). 2023 Oct 1;29(5):1401-1417.

Diabetes related neuropathy - Treatment-induced neuropathy

- Treatment-induced neuropathy of diabetes develops acutely in patients who have rapid improvement in glycemic control after a period of prolonged hyperglycemia.
- Within 8 weeks of a significant change in hemoglobin A1C, affected patients experience sudden onset of severe, burning, or shock like pain that can be length dependent or diffuse.
- Damage to small nerve fibers

Diabetes related neuropathy - Treatment-induced neuropathy

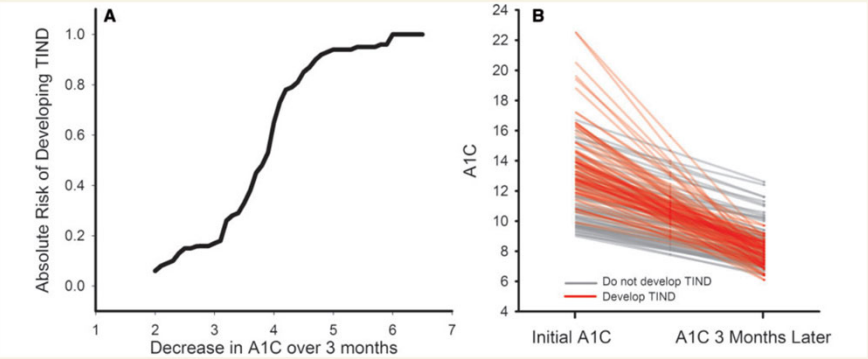

Figure 3 Risk of developing TIND. (**A**) A survival curve plotting the total number of patients (n = 168) with a decrease in HbA1c of ⩾2% over 3 months. The absolute risk of developing TIND is plotted against the change in HbA1c over a 3-month period of time. (**B**) Individual data lines for all 168 individuals with a change in HbA1c ⩾2% over 3 months. Individuals that develop TIND are shown with red lines and those that do not develop TIND are shown with grey lines.

Gibbons CH, Freeman R. Brain. 2015 Jan;138(Pt 1):43-52.

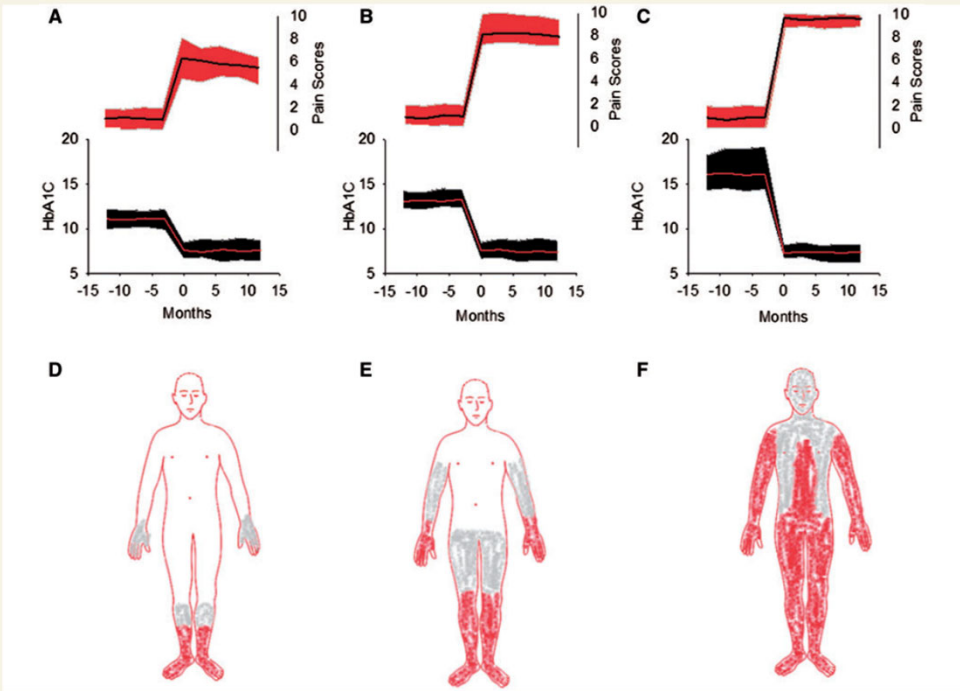

Figure 2 Complications and risks associated with TIND. (**A–F**) The 104 individuals with TIND are grouped by change in glycosylated HbA1c scores. (**A**) The 27 individuals with a decrease in HbA1c of 2–3.9% are shown. (**B**) The 52 individuals with a decrease in HbA1c of 4–7% are shown. (**C**) The 25 individuals with a decrease in AbA1c of >7% are shown. (**A–C**) The lower portion of the graph (left *y*-axis) reveals the glycosylated haemoglobin (HbA1c) scores over time. The mean value is shown in red and the standard deviation in black. The upper portion of the graph (right *y*-axis) reveals neuropathic pain scores during the same time frame. The mean value is shown in black and the standard deviation in red. The representative distribution of neuropathic is shown in **D–F**, with the area in red representing pain common to all individuals, and the area in grey common to many individuals. (**D**) The least widespread pain distribution in the individuals with the smallest change in HbA1C (corresponding to **A**). (**E**) The pain distribution in the individuals with moderate decreases in HbA1C (**B**). (**F**) The group with the largest decrease in HbA1C (**C**) has widespread neuropathic pain.

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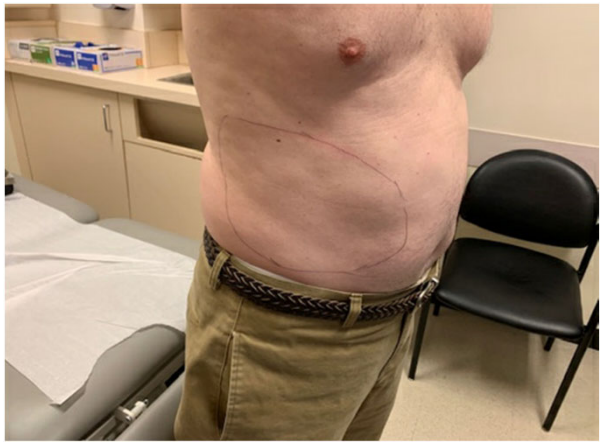
Diabetes related neuropathy - Case 5

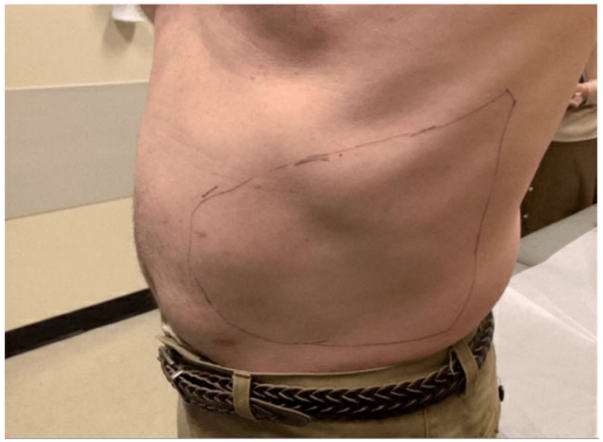
A 63-year-old man presented to the clinic with complaints of abdominal pain.

In April 2019, he experienced the sudden onset of a burning sensation on both his right and left flanks. The intensity of his symptoms has fluctuated over time, largely depending on medication, but has remained relatively constant since their onset. He has not noticed any abdominal bulging.

He has consulted multiple physicians, and at one point, his appendix was suspected as the cause. Due to abnormal imaging, he underwent an appendectomy, followed by a cholecystectomy, neither of which alleviated his symptoms.

Although there is a family history of diabetes, he does not have the condition himself. His hemoglobin A1c was 5.8% on September 20, 2019.





Diabetes related neuropathy - Truncal neuropathy

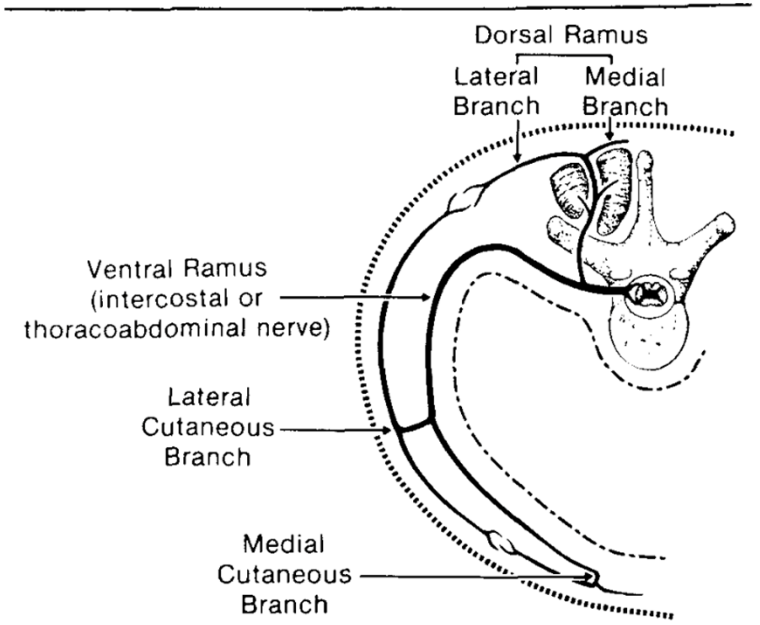


Fig 1. Course and branches of a thoracic spinal nerve. The outer stippled line *represents the skin; the* inner stippled line *is the pleura or peritoneum. (From Stewart JD. Focal peripheral neuropathies. New York: Elsevier, 1987. With permission.)*

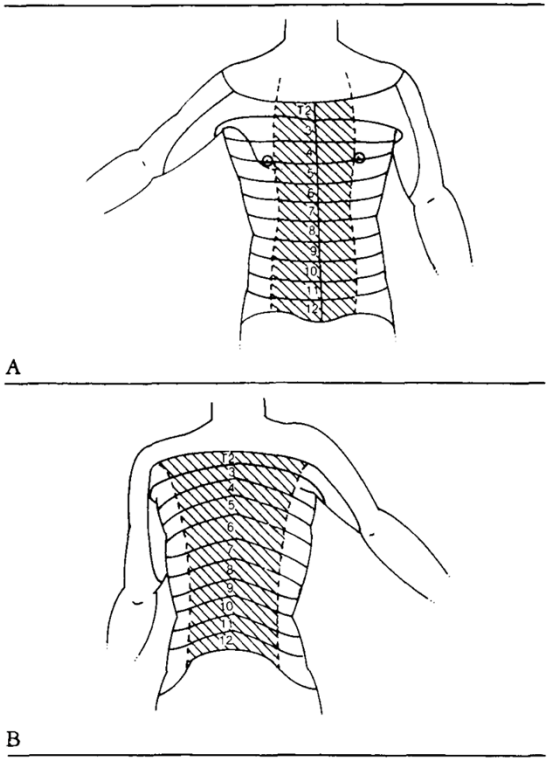


Fig 2. The cutaneous distribution of the thoracic spinal nerves {12–14}. (A) Anterior, (B) posterior.

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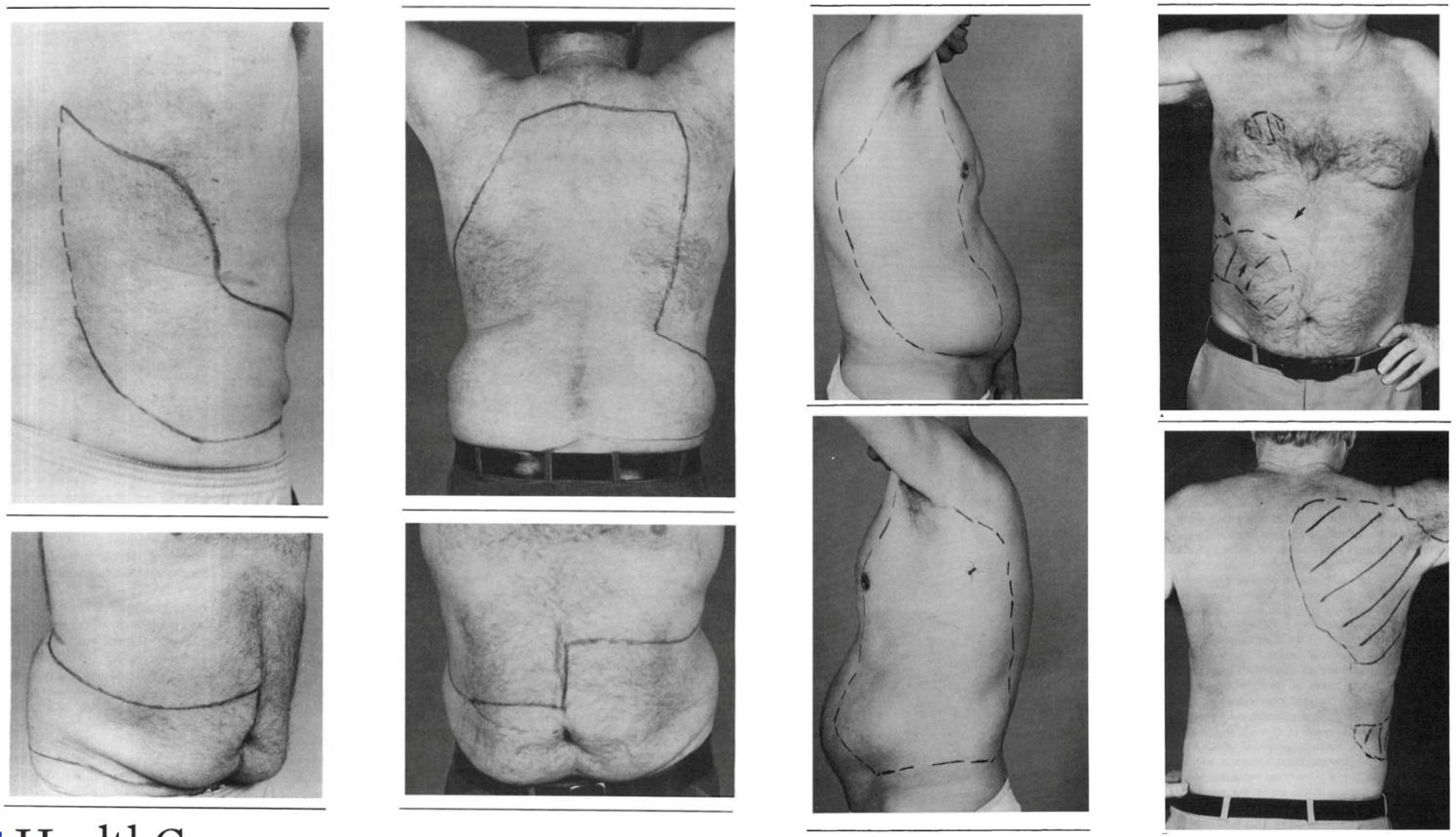
Stewart JD. Ann Neurol 1989;25:233-238

Diabetes related neuropathy - Truncal neuropathy



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Stewart JD. Ann Neurol 1989;25:233-238

In Summary

- *Diagnostic approach in neuropathic disorders*
- *Red flags that warrant a referral to neurology.*
- *Five phenotypes of diabetes-related neuropathy.*