



Neurologic Complications of Diabetes

Polyneuropathy and More

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Background

Neuropathy: Any damage to the peripheral nervous system

- Affects 2% of all people, 15% of those age 40 and over
- Diabetes is the most common underlying etiology
- 50% of diabetics have neuropathy by 25 years after onset
- 10%–100% have subclinical peripheral polyneuropathy, depending on study
- Type 1 appears to have higher risk in adolescents — 26% vs. 8% of Type 2
- Can appear in prediabetes as well



Poll

How many of your patients have diabetic neuropathy?

A. 0%

B. 1%–25%

C. 26%–50%

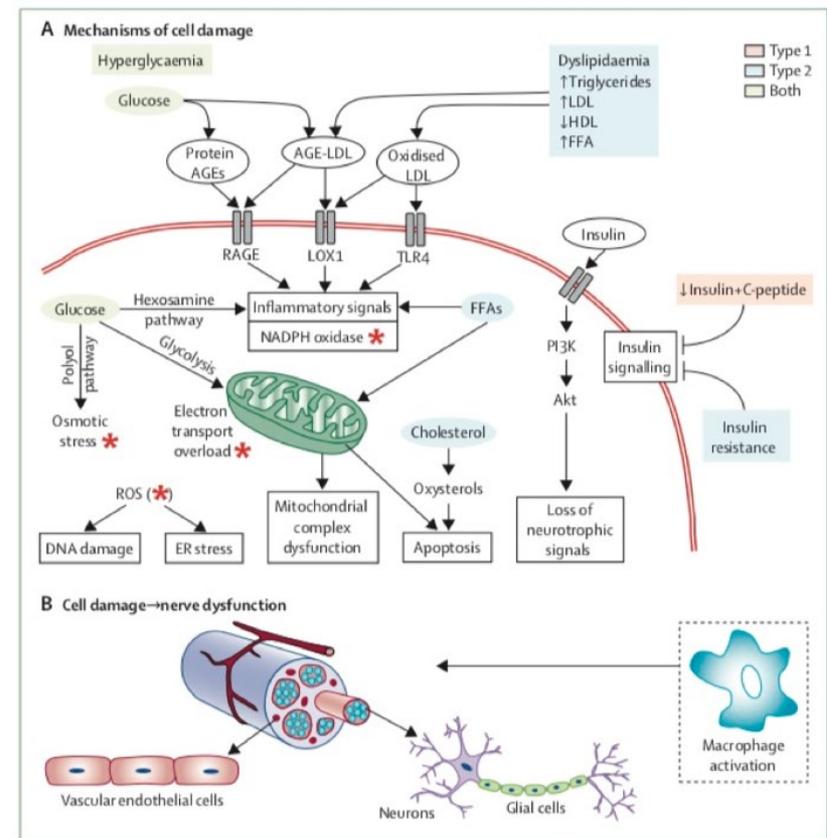
D. 51%–75%

E. 76%–99%

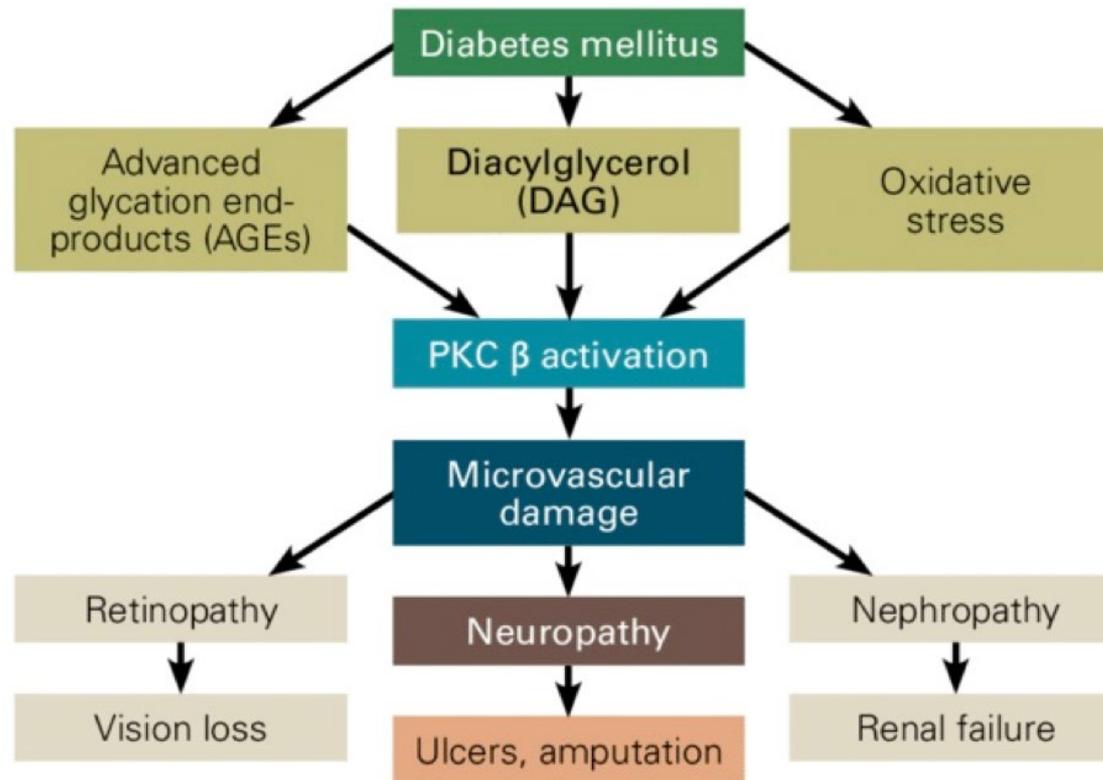
F. 100%

Pathogenesis

- Multiple pathways to damage in a cell:
- Osmotic stress, reactive oxygen species, glycolysis overload, AGE-induced inflammation, and loss of nerve repair factors like nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, insulin-like growth factor, and VEGF. Insulin (missing in T1DM) is also neurotrophic factor.
- Callaghan BC et al. “Diabetic neuropathy: clinical manifestations and current treatments.” *Lancet Neurol*, 2012; 11: 521–34

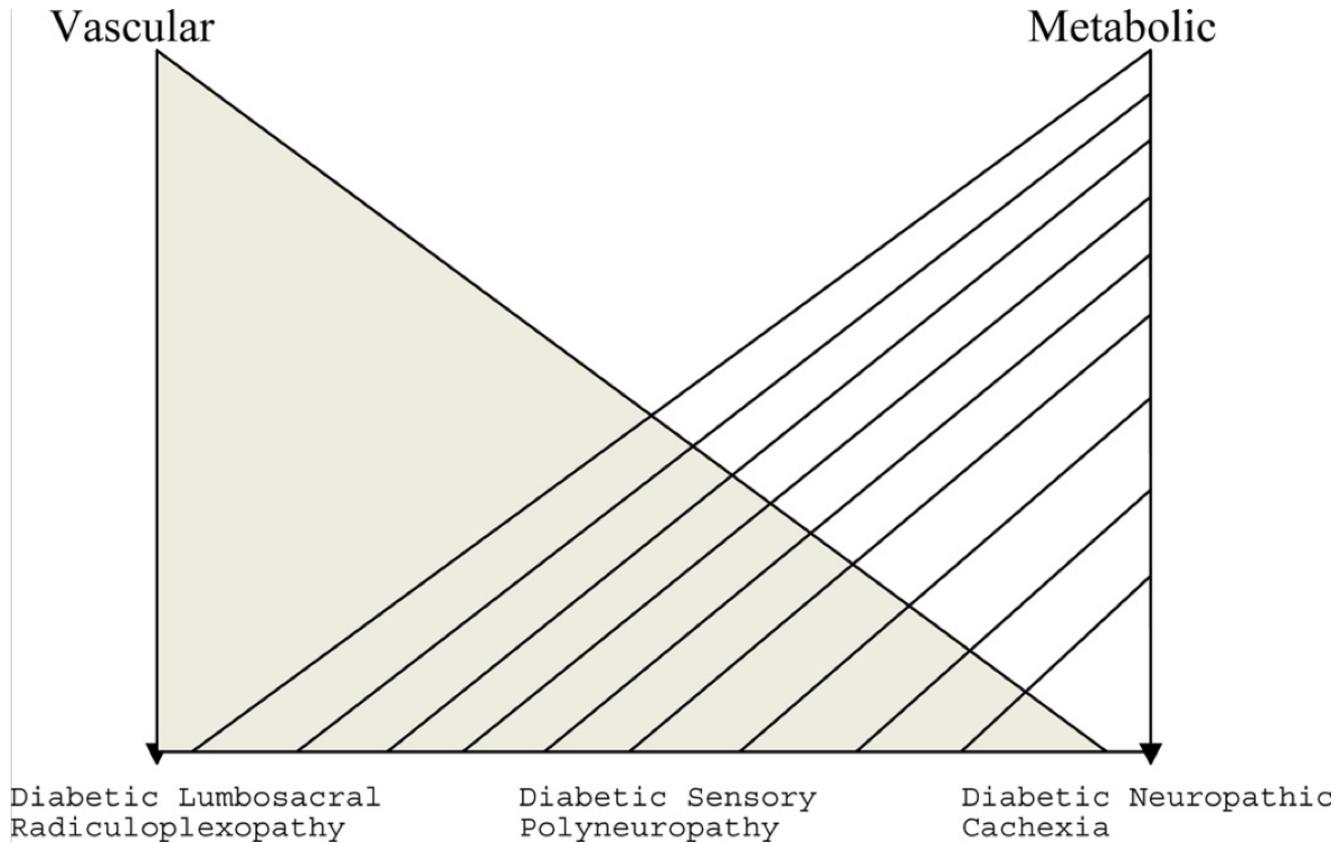


Pathogenesis (2)



Stirban A et al. Benfotiamine: Commentary and Update on Recent Studies. Diabetes, Stoffwechsel und Herz 2014; 23; 203–206.

Pathogenesis (3)



A spectrum of impact accounts for the variety of diseases seen

Classification of Diabetic Neuropathies

Symmetric

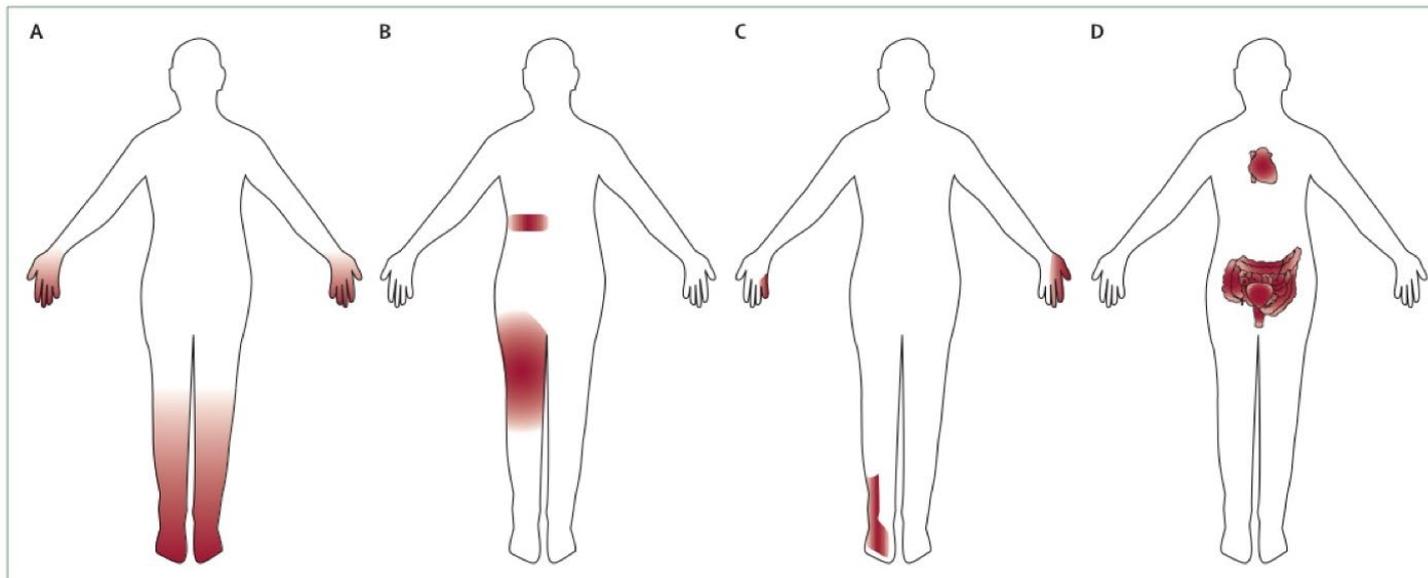
Polyneuropathies:

- **Progressive:**
 - Length-dependent polyneuropathy
 - Autonomic neuropathy
- **Episodic:**
 - Diabetic neuropathic cachexia
 - Treatment-induced diabetic neuropathy

Asymmetric, Focal, and Multifocal neuropathies:

- Diabetic radiculoplexopathy (diabetic amyotrophy; proximal diabetic neuropathy)
- Thoracic radiculopathy
- Cranial neuropathies
- Mononeuropathy

Classification of Diabetic Neuropathies (2)



Callaghan BC et al. "Diabetic neuropathy: clinical manifestations and current treatments." *Lancet Neurol* 2012; 11: 521–34

Length-dependent Polyneuropathy

- Sensory:
 - Stocking-glove pattern
 - Positive: burning, tingling, extra-sensitive
 - Negative: numbness
 - Worse at rest, nocturnal exacerbation
 - Imbalance: 2–3 times fall risk
- Motor:
 - Mild or absent
 - Foot muscle atrophy
 - Not proximal
- Absent or reduced tendon reflexes



Poll: Length-dependent Neuropathy

How many of your patients have length-dependent neuropathy?

- A. 0%
- B. 1%–25%
- C. 26%–50%
- D. 51%–75%
- E. 76%–99%
- F. 100%

Length-dependent Polyneuropathy (2)

- Exclude other causes

Russell JW et al. "Diabetic neuropathies."
Neurology Continuum 2014; 20 (5): 1226-1240

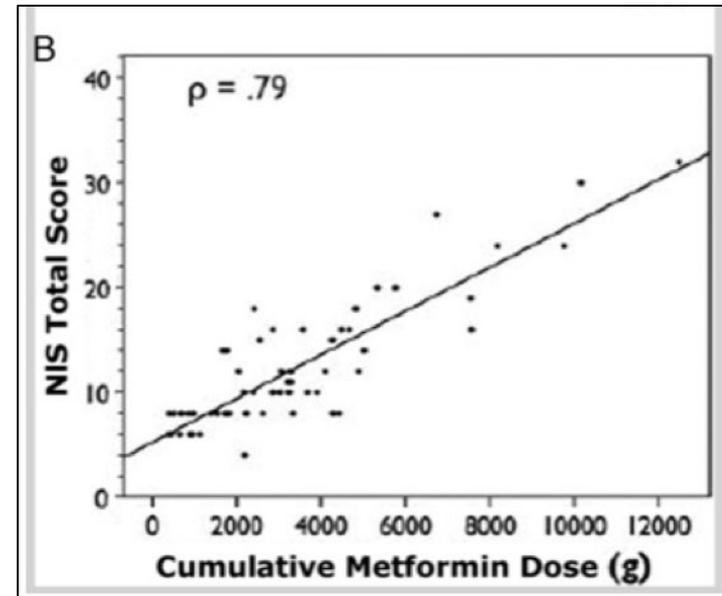
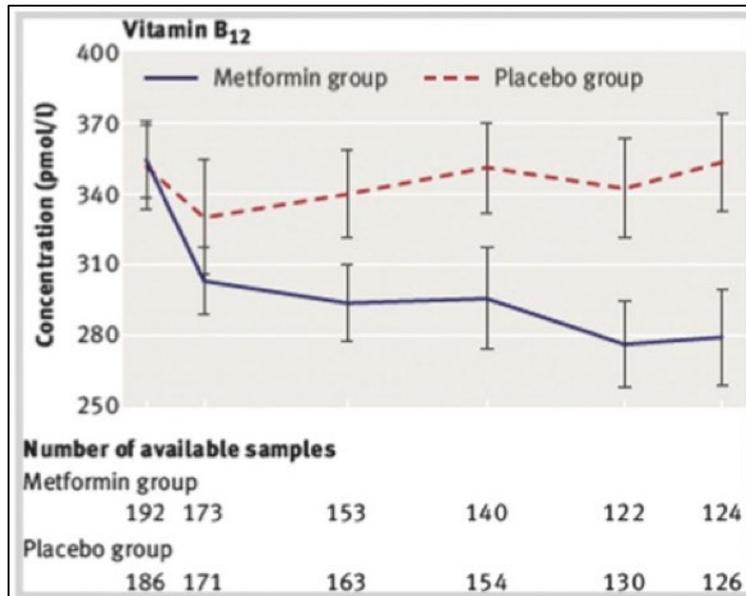
TABLE 3-3 Some Mimickers of Diabetic Neuropathy

- ▶ **Distal axonal neuropathies**
 - Vitamin B₁₂ deficiency
 - Monoclonal gammopathies
 - Vasculitis
 - Infectious causes
 - Lymphoproliferative disorders
 - Paraneoplastic diseases
- ▶ **Small fiber neuropathies (many of these diseases can also cause large fiber neuropathies)**
 - Alcoholism
 - HIV
 - Monoclonal gammopathy
 - Pharmacologic or environmental toxins
 - Sjögren syndrome
 - Systemic or familial amyloidosis
 - Sarcoidosis
 - Hereditary sensory neuropathy
 - Other inherited neuropathies
- ▶ **Demyelinating neuropathy**
 - Chronic inflammatory demyelinating polyradiculoneuropathy and other demyelinating neuropathies
- ▶ **Multifocal neuropathy**
 - Other causes of mononeuropathy multiplex
- ▶ **Radiculopathy and plexopathies**
 - Sarcoidosis
 - Amyloidosis
 - Vasculitis
 - Neoplastic and paraneoplastic causes

HIV = human immunodeficiency virus.

Length-dependent polyneuropathy

Check vitamin B12 and metabolites with metformin use and decline



de Jager J et al. "Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial." *BMJ* 2010; 340: c2181.

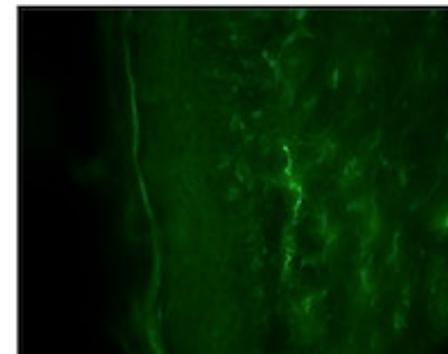
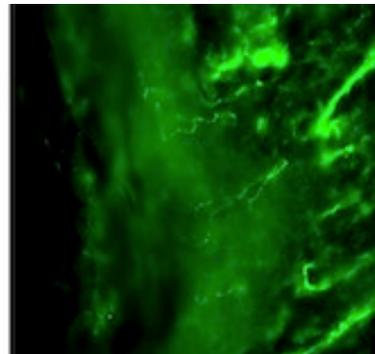
Wile DJ, Toth C. Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy. *Diabetes Care* 2010; 33 (1): 156Y161

Length-dependent polyneuropathy

Intraepidermal nerve fiber density testing

IENF Density Mean (fibers/mm)

Diabetic	Controls
5.4(\pm 6.7)	15.7(\pm 17.8)

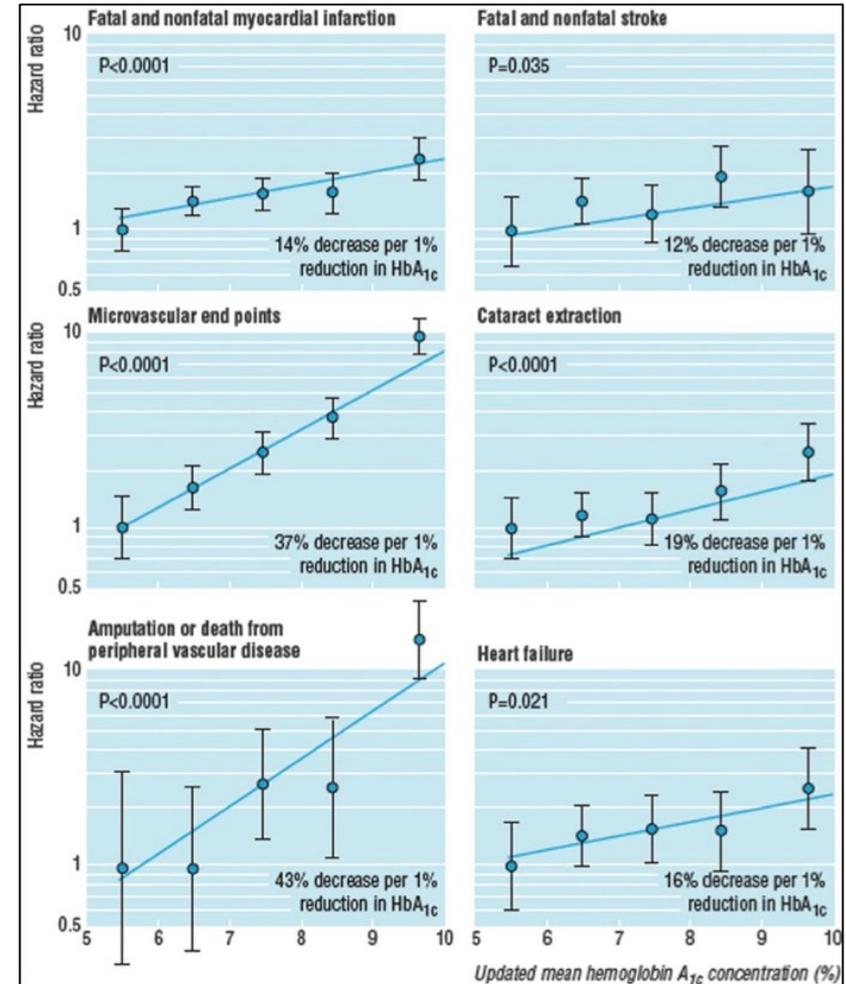


Length-dependent Polyneuropathy

Glycemic Control

- **Glycemic control**
- Pain control
- Nerve therapy

Stratton IM et al. "Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study." *BMJ* 2000; 321 (7258): 405Y412



Length-dependent Polyneuropathy Pain Control

- Glycemic control
- **Pain control**
- Nerve therapy

Callaghan BC et al. “Diabetic neuropathy: clinical manifestations and current treatments.” *Lancet Neurol* 2012; 11: 521–34

	EFNS ⁷²	AAN ⁷⁴
Pregabalin (300–600 mg a day)	A	A
Gabapentin	A	B
Lamotrigine	A/B*	B†
Oxcarbazepine	A/B*	B†
Lacosamide	A/B*	B†
Sodium valproate	A/B*	B
Tricyclic antidepressants	A	B (amitriptyline)
Serotonin-norepinephrine reuptake inhibitor	A	B (venlafaxine, duloxetine)
Opioids	A (oxycodone)	B (morphine, oxycodone)
Tramadol	A	B
Dextromethorphan	B	B
Topical capsaicin	A/B*	B
Isosorbide spray	A	B
ABT-594	A	..
Botulinum toxin	B	..
Levodopa	B	..
Lidocaine patch	..	C

EFNS=European Federation of Neurological Societies task force. AAN=American Academy of Neurology. A=established as effective. B=probably effective. C=possibly effective. *Drug classed as ineffective or with discrepant results. †Drug not recommended.

Table 3: Comparison of EFNS and AAN guidelines for pharmacological treatment of diabetic neuropathic pain

Length-dependent Polyneuropathy

Pain Control (cont.)

- Glycemic control
- **Pain control**
- Nerve therapy

Callaghan BC et al. “Diabetic neuropathy: clinical manifestations and current treatments.” *Lancet Neurol* 2012; 11: 521–34

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Table 3: Comparison of EFNS and AAN guidelines for pharmacological treatment of diabetic neuropathic pain



Poll: Medications

Which pain medications do you use most?

- A. Gabapentin
- B. Pregabalin
- C. TCAs (amitriptyline, nortriptyline, etc.)
- D. SNRIs (duloxetine, venlafaxine)
- E. Topicals (capsaicin, lidocaine, etc.)
- F. Combination therapy



Length-dependent Polyneuropathy Nerve Therapy

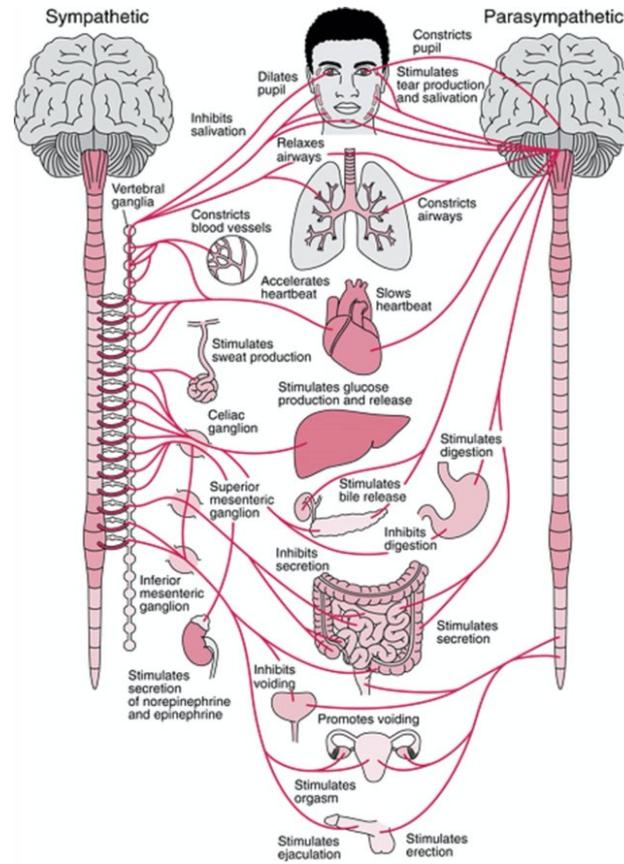
- Glycemic control
 - Pain control
 - **Nerve therapy**
- **Viomed – VM202:**
 - Phase III trial, with estimated completion 6/2019.
 - Double-blind, randomized, placebo-controlled, multicenter study
 - Hepatocyte growth factor with potential neurotrophic effect
 - **Vertex – VX-150:**
 - 3rd Phase II trial was successful 12/2018.
 - NaV1.8 sodium channel inhibitor
 - Found in dorsal root ganglion and unmyelinated C-fibers for nociception

Autonomic Neuropathy

Sympathetic

“Fight or flight”

- Activating
- Increases heart rate
- Dilates pupil
- Inhibits GI activity
- Closes sphincters
- Increases sweating
- Diverts blood from skin and GI tract to skeletal muscles



Parasympathetic

“Rest and digest”

- Relaxing
- Lowers heart rate
- Constricts pupil
- Promotes digestion, GI peristalsis
- Empties bladder
- Relaxes sphincters
- Mediates genital erection

Autonomic Neuropathy (2)

TABLE 3-2 Symptoms and Tests for Aspects of Diabetic Dysautonomia

Category	Symptoms/Signs	Diagnostic Tests
Cardiovascular	Orthostasis	Heart rate variation to deep breathing/Valsalva maneuver
	Arrhythmia	
	Silent ischemia	Blood pressure variability to grip, standing, tilt
	Reduced exercise tolerance	PET cardiac scintigraphy
Gastrointestinal	Nausea	Gastric emptying study
	Early satiety	Colonoscopy
	Constipation/diarrhea	
Genitourinary	Erectile dysfunction	Nocturnal penile plethysmography
	Retrograde ejaculation	Postvoid residual
	Reduced vaginal lubrication	
	Neurogenic bladder	
Cutaneous/sudomotor	Anhidrosis	Quantitative sudomotor axon reflex testing
	Dry skin	Sympathetic skin response
	Heat intolerance	Thermoregulatory sweat testing
Pupillary	Argyll Robertson pupil	
Central, integrative	Hypoglycemic unawareness	
	Reduced hypoxia-induced ventilatory drive	

Smith AG, Singleton JR. Neurology Continuum 2012; 18 (1): 60–84



Poll: Autonomic Neuropathy

How many of your patients have autonomic neuropathy?

- A. 0%
- B. 1%–25%
- C. 26%–50%
- D. 51%–75%
- E. 76%–99%
- F. 100%

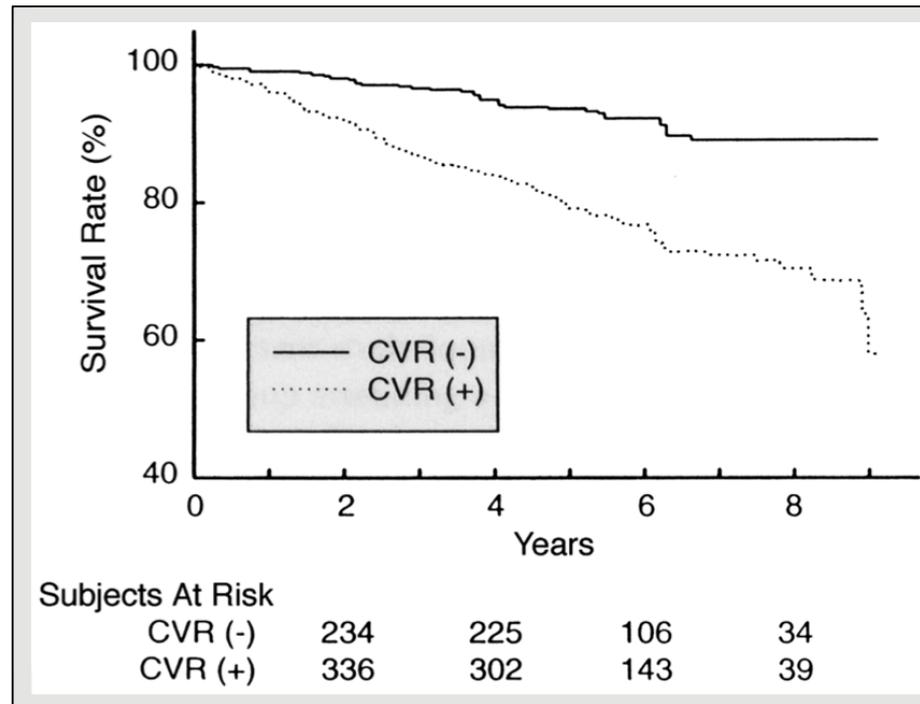


Autonomic Neuropathy (3)

- Clinically seen in 5%–35% of diabetics
- Vagus nerve often affected first
- Subclinical autonomic dysfunction is very common
- Mild dysfunction in up to 75% of those with length-dependent polyneuropathy
- Marker of adverse cerebrovascular, cardiovascular, and renal outcomes

Autonomic Neuropathy

Five-year mortality rate is 2–5 times higher



Chen HS et al. "Abnormal cardiovascular reflex tests are predictors of mortality in type 2 diabetes mellitus." *Diabet Med* 2001; 18 (4): 268Y273

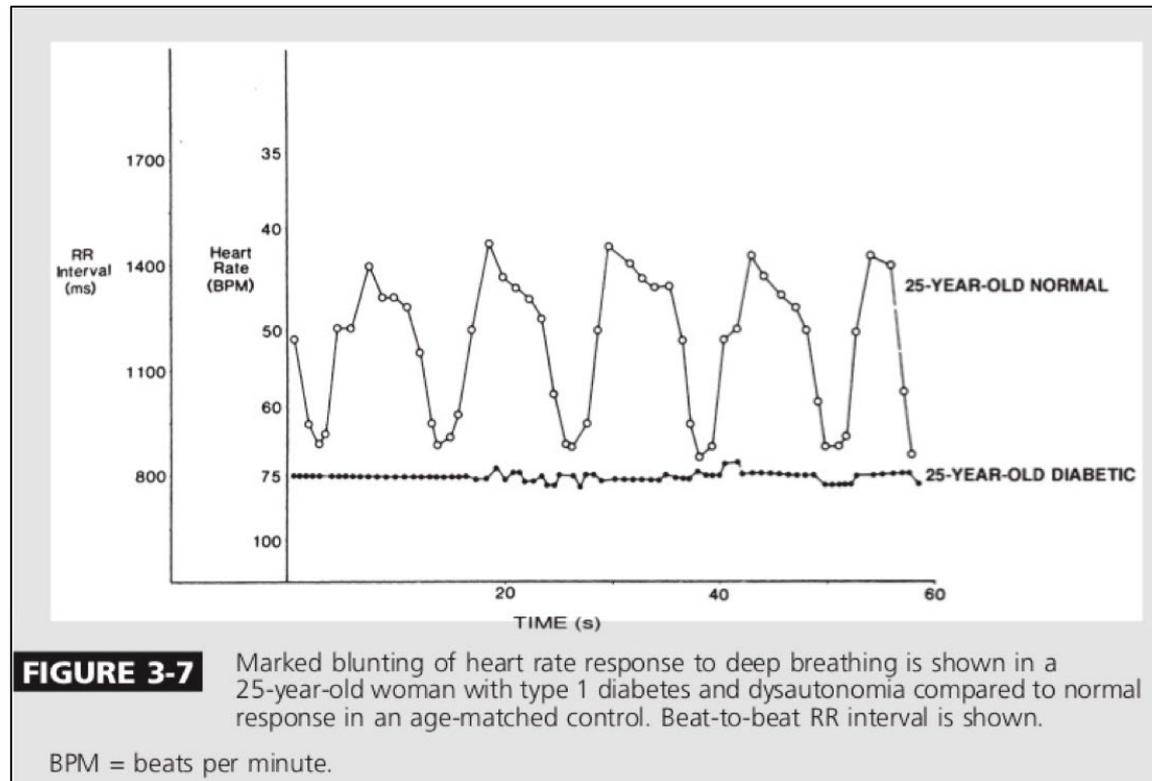


Autonomic Neuropathy (4)

Cardiac

- Heart rate changes
 - Impaired HR variability
 - Resting tachycardia, postural tachycardia, fixed bradycardia
- Blood pressure changes
 - Orthostatic hypotension
 - Postprandial hypotension
 - Nocturnal hypertension
- Limited exercise tolerance

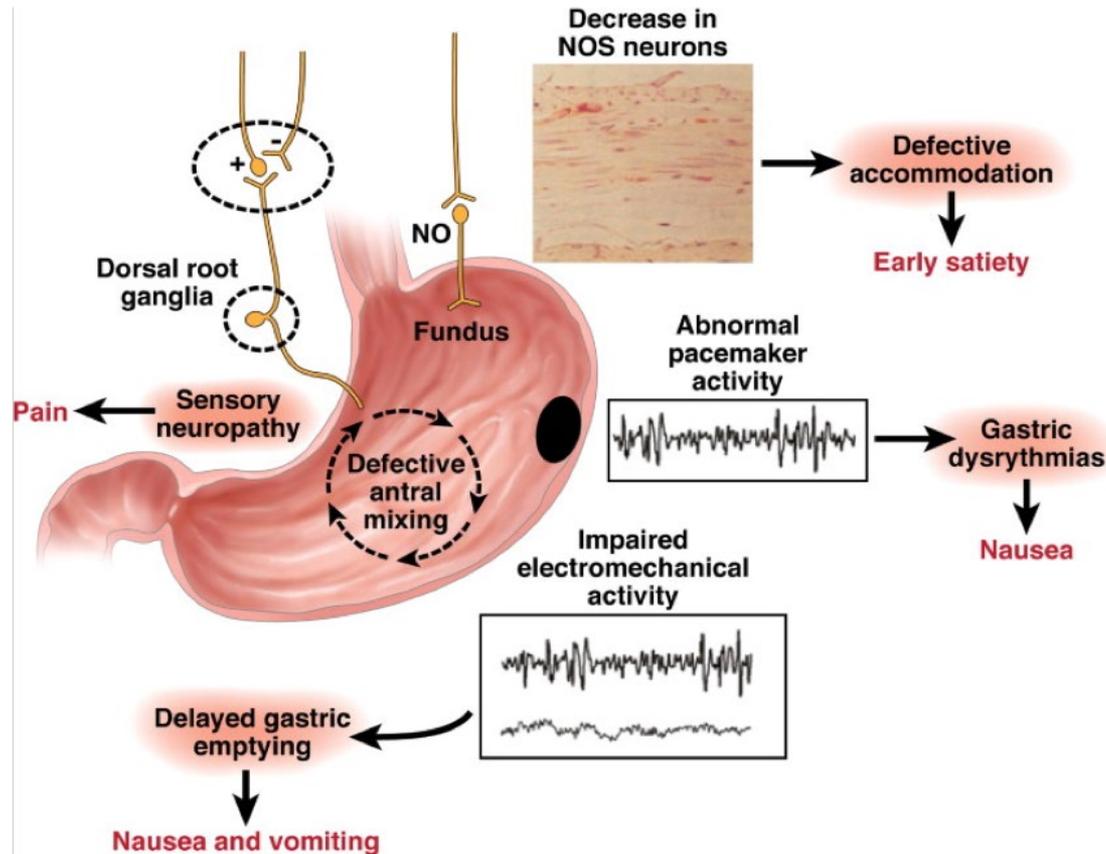
Autonomic Neuropathy (5)



Dyck PJ, Thomas PK, editors. Diabetic neuropathy. 2nd ed. Philadelphia: Saunders, 1999: 177.

Autonomic Neuropathy

Gastrointestinal



Owyang, C. "Phenotypic Switching in Diabetic Gastroparesis: Mechanism Directs Therapy." *Gastroenterology*; 2011; 141 (4); 1134–1137

Autonomic Neuropathy

Gastrointestinal (cont.)

Symptoms	Mechanisms	Therapeutic Approaches
Early satiety and postprandial fullness	Defective accommodation	NO donors
Nausea and vomiting	Gastroparesis secondary to enteric nervous system neuropathy	Prokinetic agents (?) Gastric pacing
Epigastric pain	Sensory neuropathy	Tricyclics (?) Neurostimulation
Persistent nausea	Tachygastria	Control of blood glucose Domperidone

Owyang, C. “Phenotypic Switching in Diabetic Gastroparesis: Mechanism Directs Therapy.” *Gastroenterology*; 2011; 141 (4); 1134–1137



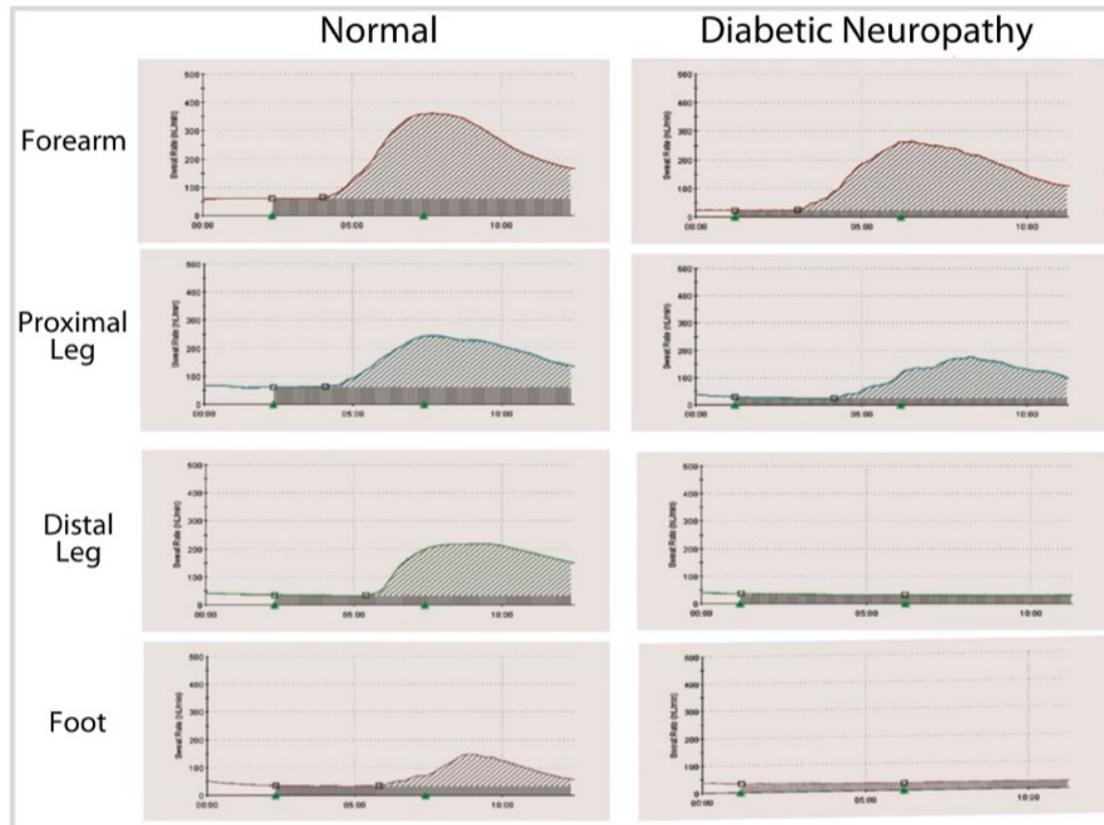
Autonomic Neuropathy (6)

Sudomotor

- Excessive coldness
- Blue/white skin discoloration
- Impaired sweating
- Dry and cracking skin

Autonomic Neuropathy

Sudomotor — QSART



Russell JW et al. "Diabetic neuropathies." *Neurology Continuum* 2014; 20 (5): 1226–1240

Autonomic Neuropathy

Sudomotor — SudoScan

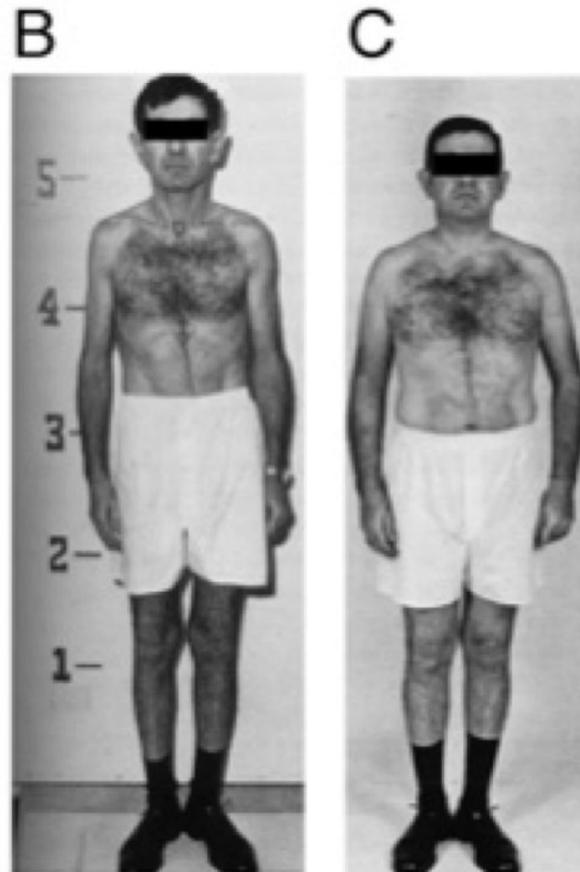




Neuropathic Cachexia (1)

- Onset with poor glycemic control
- More often older men, but can happen at any age
- Truncal involvement
- Depression
- Weight loss and pain go together
- Improves over weeks to months with tight glycemic control
- **Nutritional support is key**
- Pain control generally ineffective

Neuropathic Cachexia (2)



Treatment-induced

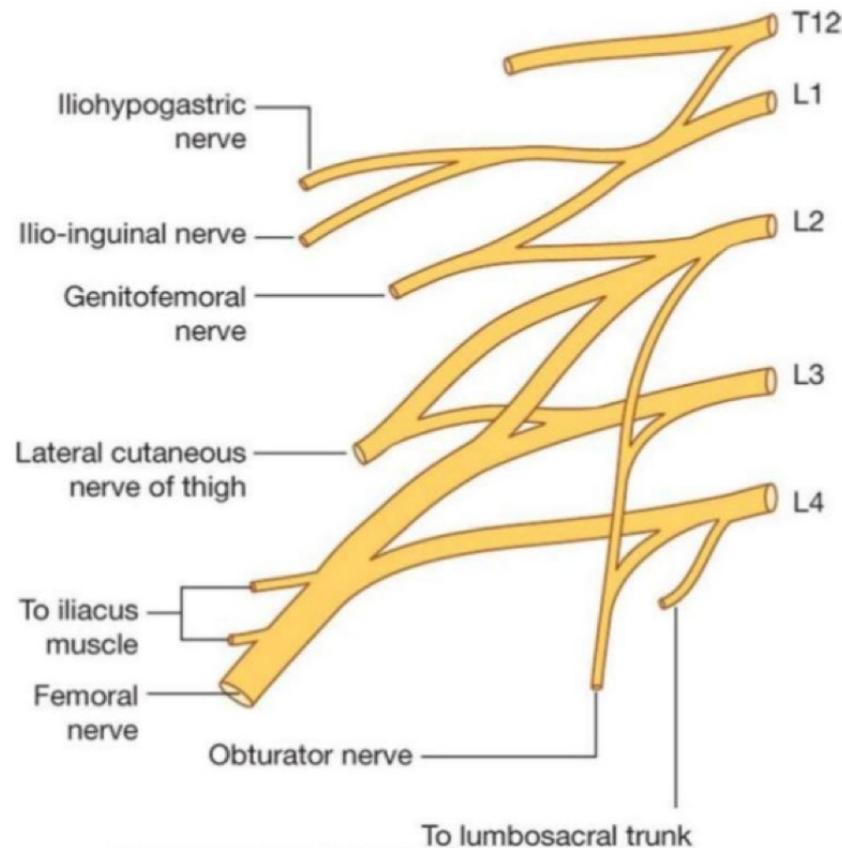
- Onset with rapidly improving glycemic control
- Sudden onset of acute severe distal pain
- Pain control is generally ineffective
- Lasts months to a year
- Typically resolves with ongoing good glycemic control
- Can have long-lasting autonomic neuropathy
 - More common in Type 1



Radiculoplexopathy

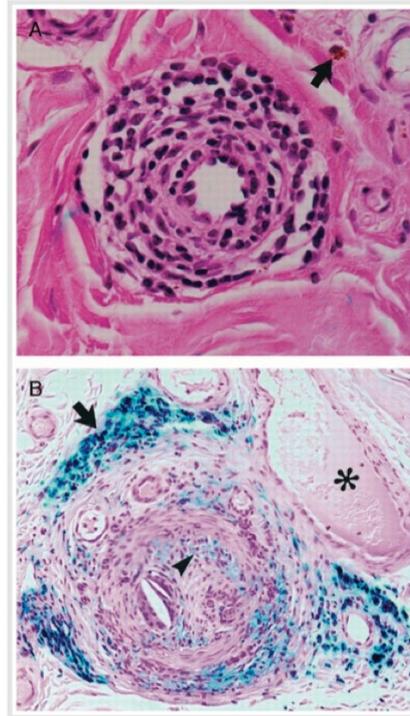
- Onset more often with rapid weight loss
- Not related to glycemic control or duration of diabetes
- Acute onset of severe pain
- Often with sensory loss as well
- Proximal weakness near onset
- Muscle atrophy, distal deficits can persist
- Spreads over limb within days to weeks
- Can often spread to the other limb within weeks
 - Typically remains asymmetric
- More often involves lower limbs
- Treatment unclear

Radiculoplexopathy (2)



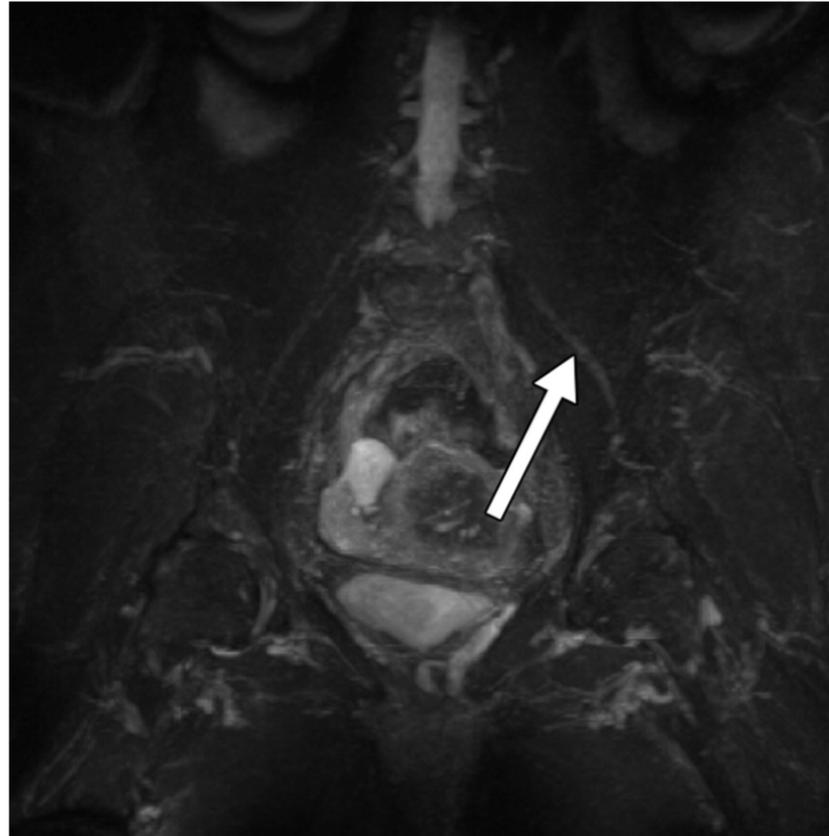
Drake: Gray's Anatomy for Students, 2nd Edition.
Copyright © 2009 by Churchill Livingstone, an imprint of Elsevier, Inc. All rights reserved.

Radiculoplexopathy (4)



Dyck PJ, et al. "Microvasculitis and ischemia in diabetic lumbosacral radiculoplexus neuropathy." *Neurology* 1999; 53(9): 2113-2121

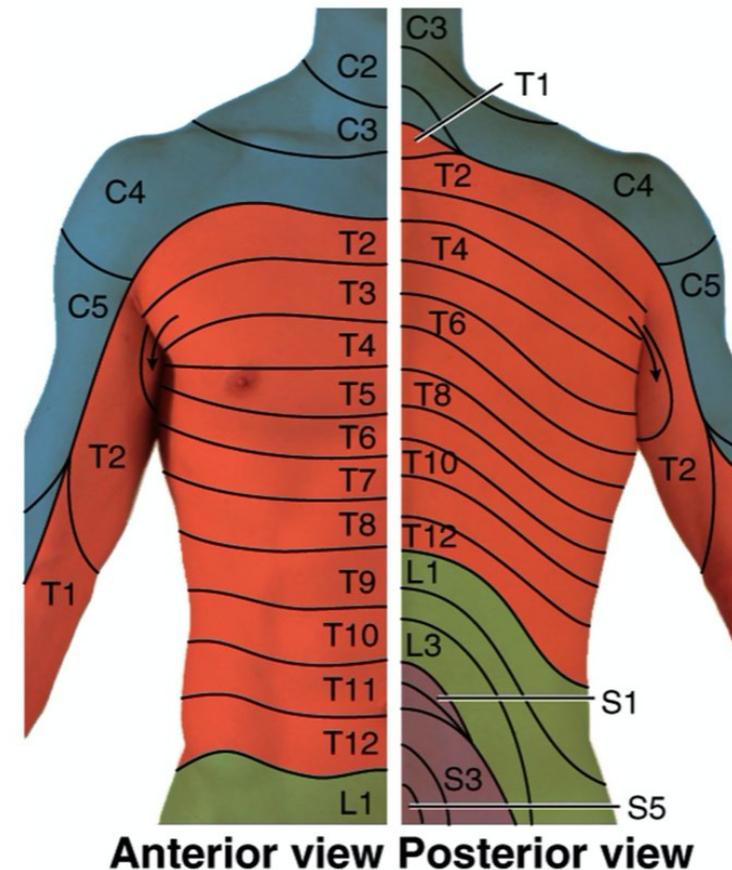
Radiculoplexopathy (5)



Thakkar RS et al, Spectrum of High-Resolution MRI Findings in Diabetic Neuropathy. American Journal of Roentgenology 2012 199:2, 407-412

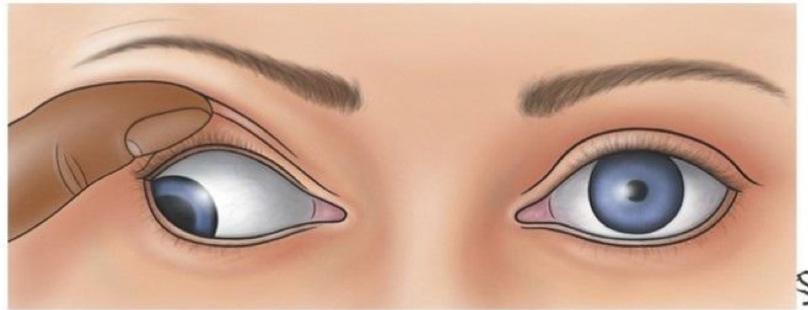
Other Mononeuropathies

- Thoracic radiculopathy
 - Painful thoracic dermatome
 - Typical pain control regimen



Other Mononeuropathies (2)

- Cranial neuropathies
 - Causes at least 10% of oculomotor palsies
 - Ptosis, impaired movement (“down & out”), diplopia, pain

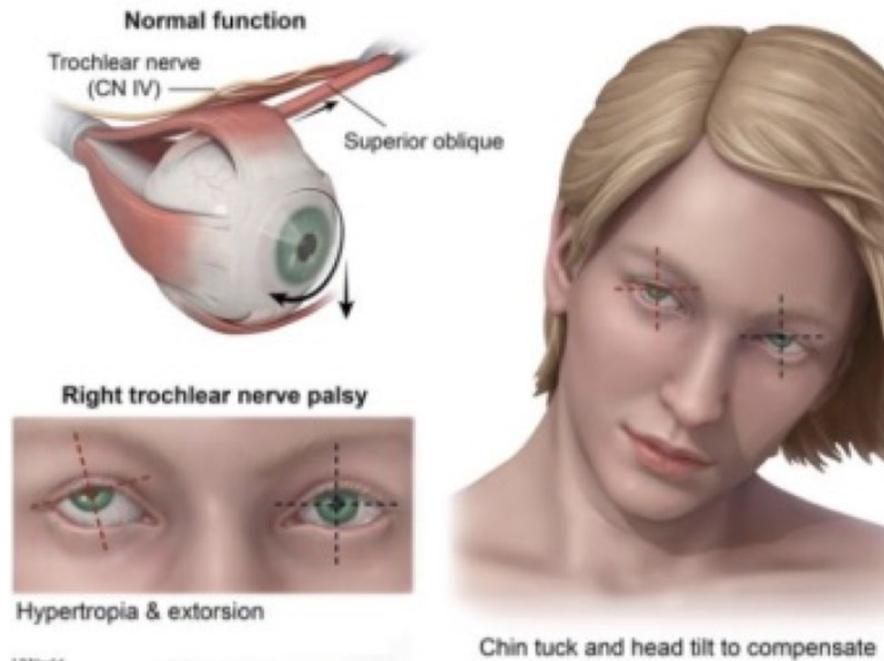


Right eye: Downward and outward gaze, dilated pupil, eyelid manually elevated due to ptosis

Left: Normal

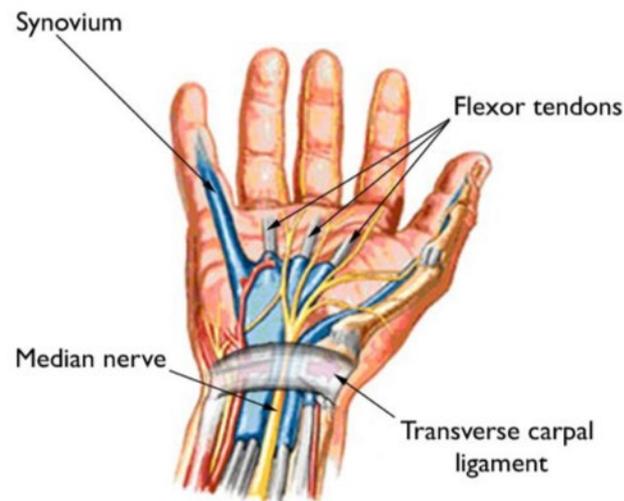
Other Mononeuropathies (3)

- Cranial neuropathies
 - DM most common cause of trochlear palsy
 - Up and out; improves with positioning



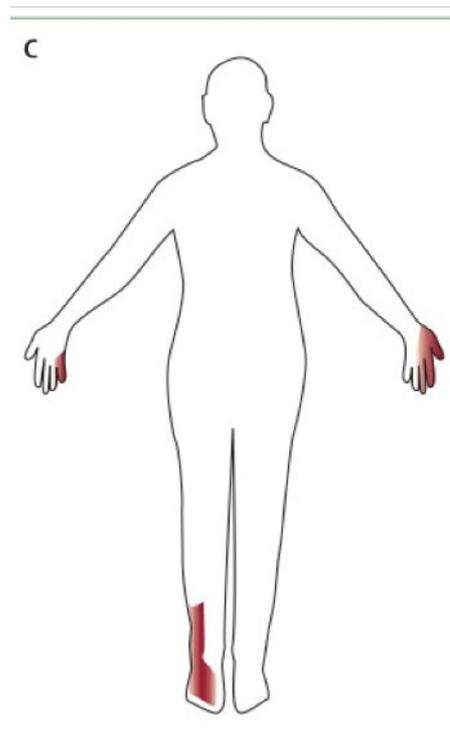
Other Mononeuropathies (4)

- Compression neuropathies
 - 2% of the general population gets carpal tunnel syndrome
 - 14% of all diabetics do
 - 30% of diabetics with length-dependent polyneuropathy do
 - Obesity may play role as well



Other Mononeuropathies (5)

- Mononeuropathy
 - Vast differential, similar to polyneuropathy
 - Should evaluate for other causes as well





Poll: Neuropathy

Which type of neuropathy do your patients have?

- A. Length-dependent neuropathy
- B. Autonomic neuropathy
- C. Acute episodic polyneuropathy
- D. Radiculoplexopathy
- E. Other mononeuropathy
- F. Combination of the above



Questions

Thank You