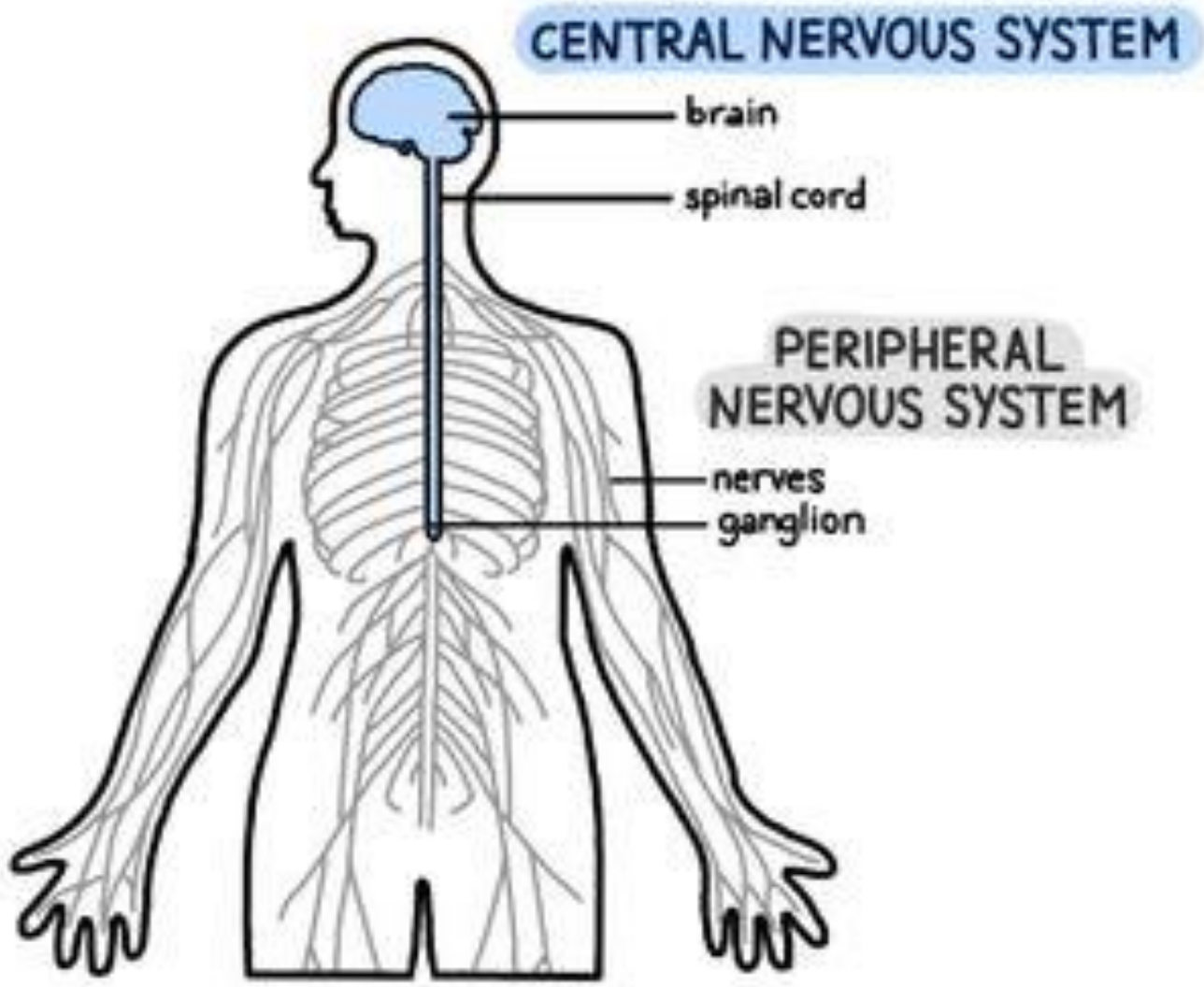
Dr. Omid Hesami

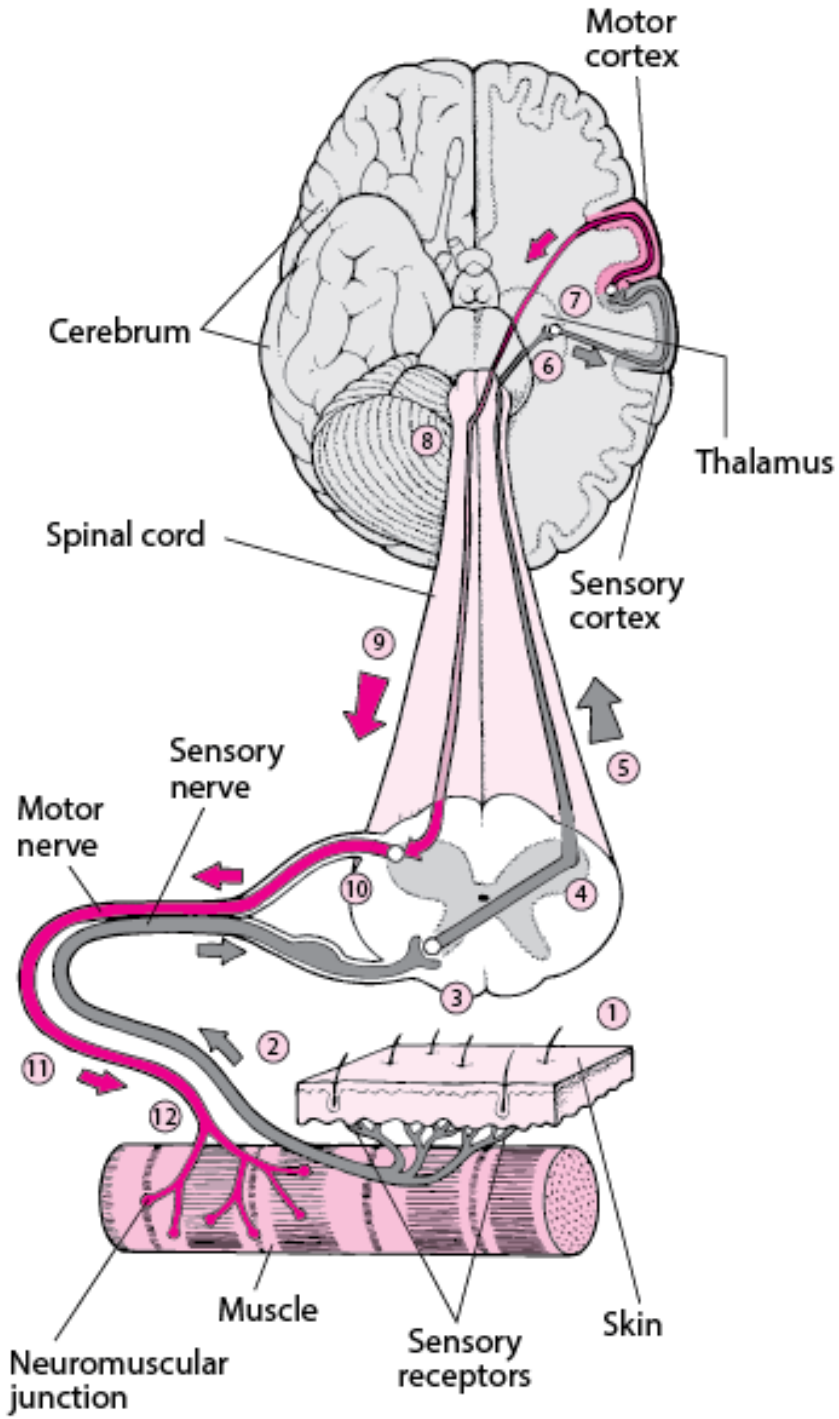
Neuromuscular fellowship

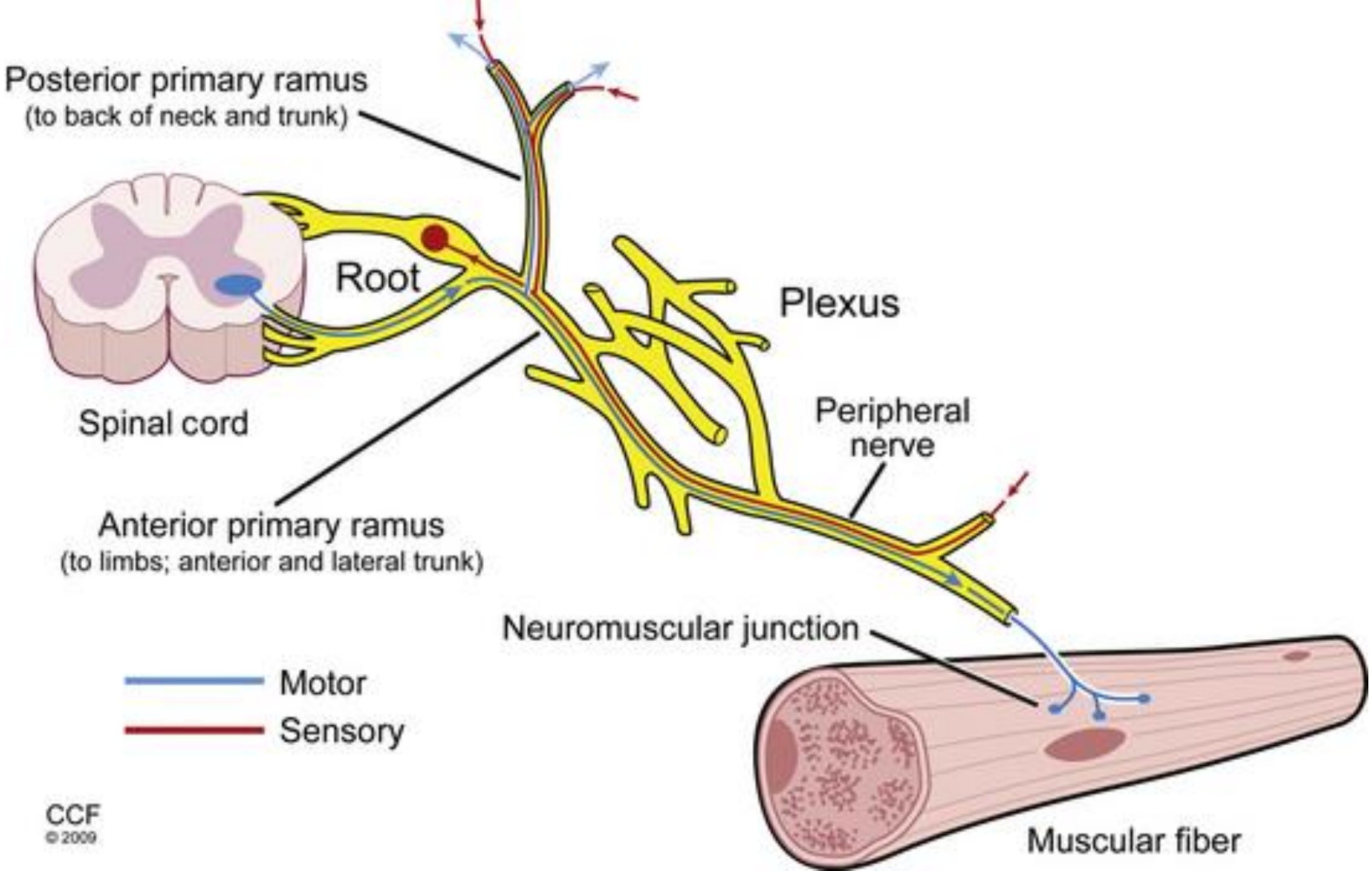
Shahid Beheshti University of Medical Sciences

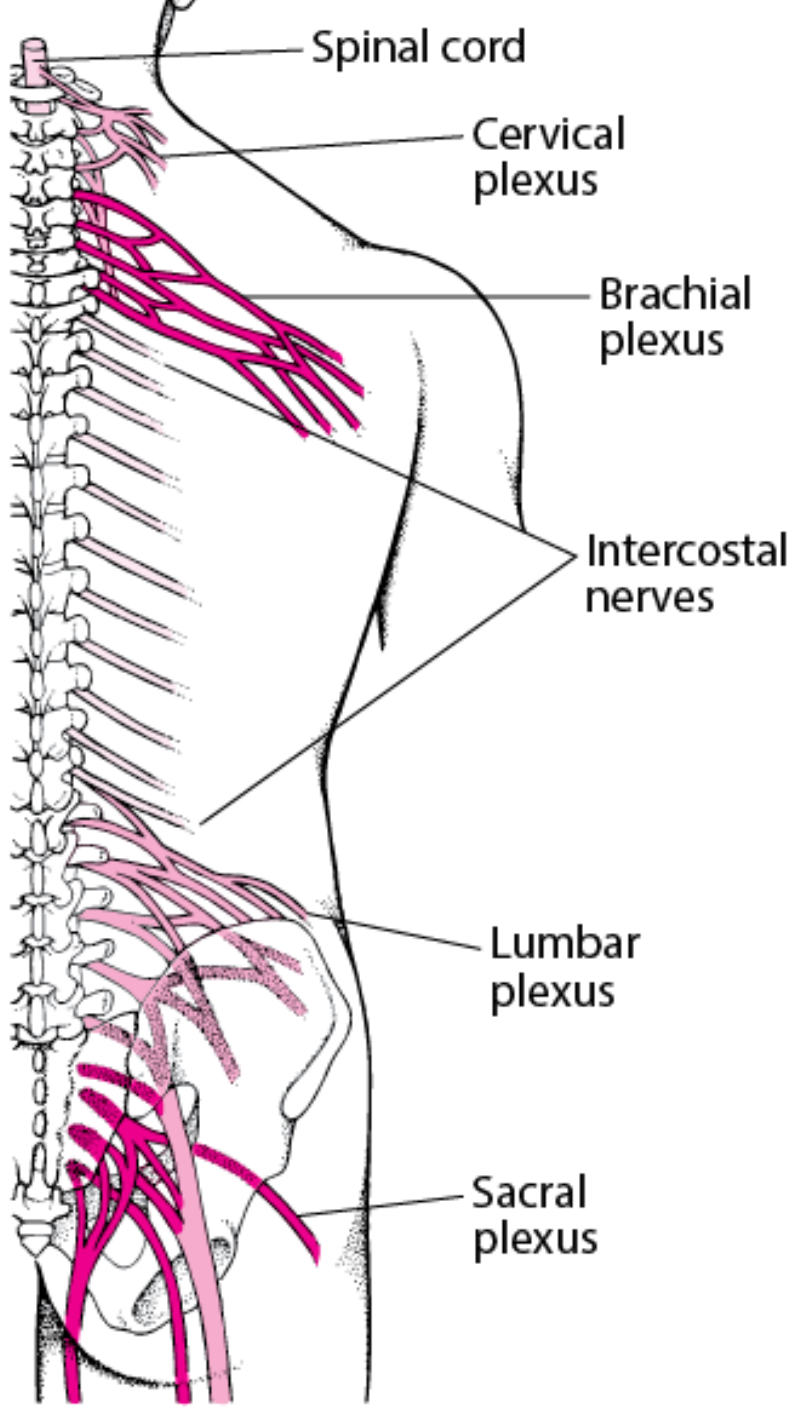
Peripheral nerve disorders

- Peripheral nerve disorders are common neurological problems caused by dysfunction of peripheral motor, sensory, or autonomic nerves.
- The causes of neuropathies are disparate and their clinical presentations highly variable. The main causes of neuropathy are entrapment, systemic diseases, inflammatory and autoimmune disorders, inherited disorders, ischemic settings, paraneoplastic conditions, deficiency states, infections, and toxins.
- A logical systematic diagnostic approach to peripheral neuropathies consists of a detailed history, comprehensive physical and neurological examinations, detailed electrodiagnostic (EDX) studies, and possibly additional ancillary testing (such as autonomic testing, skin biopsy and nerve biopsy).

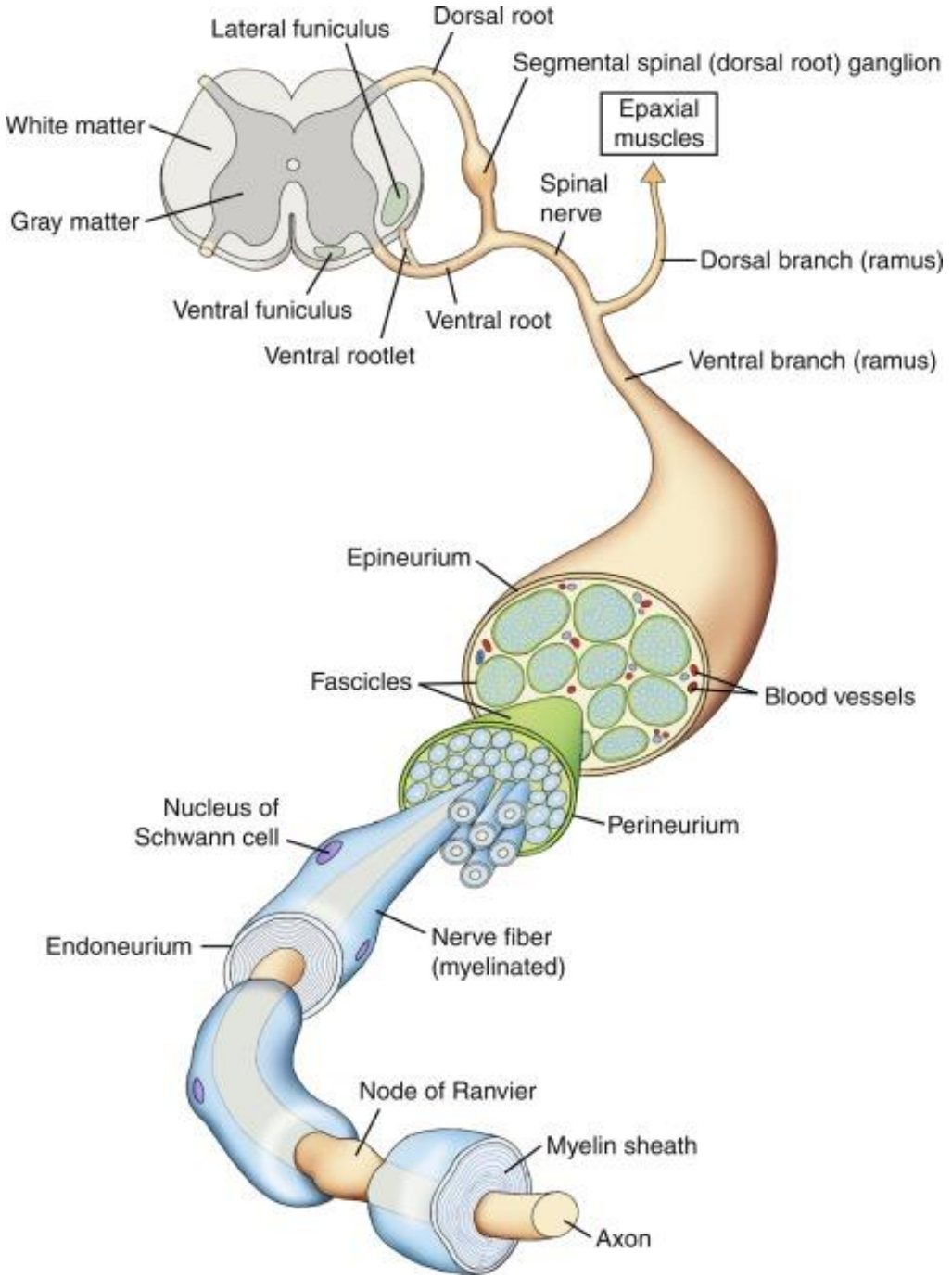

CENTRAL NERVOUS SYSTEM
brain
spinal cord
PERIPHERAL NERVOUS SYSTEM
nerves
ganglion


Motor cortex
Cerebrum
Thalamus
Spinal cord
Sensory cortex
Sensory nerve
Motor nerve
Muscle
Sensory receptors
Skin
Neuromuscular junction
1
2
3
4
5
6
7
8
9
10
11
12


Posterior primary ramus
(to back of neck and trunk)
Root
Plexus
Spinal cord
Peripheral nerve
Anterior primary ramus
(to limbs; anterior and lateral trunk)
Neuromuscular junction
Motor
Sensory
CCF
© 2009
Muscular fiber


Spinal cord
Cervical plexus
Brachial plexus
Intercostal nerves
Lumbar plexus
Sacral plexus

- The peripheral nerve is a cable-like structure containing bundles of both unmyelinated and myelinated fibers and their supporting elements.



Diabetic neuropathy

- Diabetic neuropathy is defined as the presence of symptoms and signs of peripheral nerve dysfunction in individuals with diabetes after the exclusion of other causes (vitamin B_{12} deficiency and endocrine neuropathies).
- In general, the diagnosis of a definite diabetic neuropathy should be based on clinical symptoms, objective neurological signs, and EDX confirmation.

PATHOPHYSIOLOGY OF DIABETIC NEUROPATHY

- the etiology is most likely multifactorial.
- Derangements of normal metabolic homeostasis
- Autoimmunity
- Microvascular insufficiency

Diabetic neuropathy

- Both type 1 and type 2 diabetes carry a high risk of neuropathy development.
- The prevalence of neuropathy in the population of individuals with diabetes is similar between those with type 1 and type 2 diabetes, ranging from 10% to 50%.
- The risk of developing symptomatic neuropathy in patients without neuropathic symptoms or signs at the time of initial diagnosis of diabetes is estimated to be 4% to 10% by 5 years and up to 50% by 25 years.

Diabetic neuropathy

- In a population cohort of diabetic patients, two-thirds of diabetics had objective evidence of some type of neuropathy, but only about 15% had symptomatic degrees of polyneuropathy.
- Electrophysiological studies demonstrate subclinical conduction abnormalities in most patients with IDDM after 5 to 10 years of diabetes.

Diabetic neuropathy

- Diabetics with lower-limb ischemia due to peripheral vascular disease also have a more severe neuropathy than diabetics without limb ischemia.
- Several recent studies have shown that patients presenting with a chronic “idiopathic” axonal polyneuropathy have nearly a twofold higher frequency of undiagnosed diabetes mellitus and impaired fasting blood glucose than age-matched controls.
- These studies suggest that an axonal neuropathy may be the presenting or the earliest manifestation in diabetes.

Diabetic neuropathy

- Neuropathy related to type 1 diabetes is directly linked to glycemic control.
- Optimal glycemic control in type 1 diabetes reduces the relative risk of neuropathy development by 78%.
- In contrast, although still an important risk factor, hyperglycemia is much less important in the pathogenesis of neuropathy in type 2 diabetes.
- In type 2 diabetes, intensive glycemic control only reduces the risk of neuropathy by 5% to 9%
- Increasing evidence indicates that individual components of the metabolic syndrome, including hypertriglyceridemia, hypertension, abdominal obesity, low levels of high-density lipoproteins, and tobacco use, are important determinants of neuropathy risk and progression in type 2 diabetes

BOX 107.14 Classification of Diabetic Neuropathies

GENERALIZED SYMMETRICAL POLYNEUROPATHIES

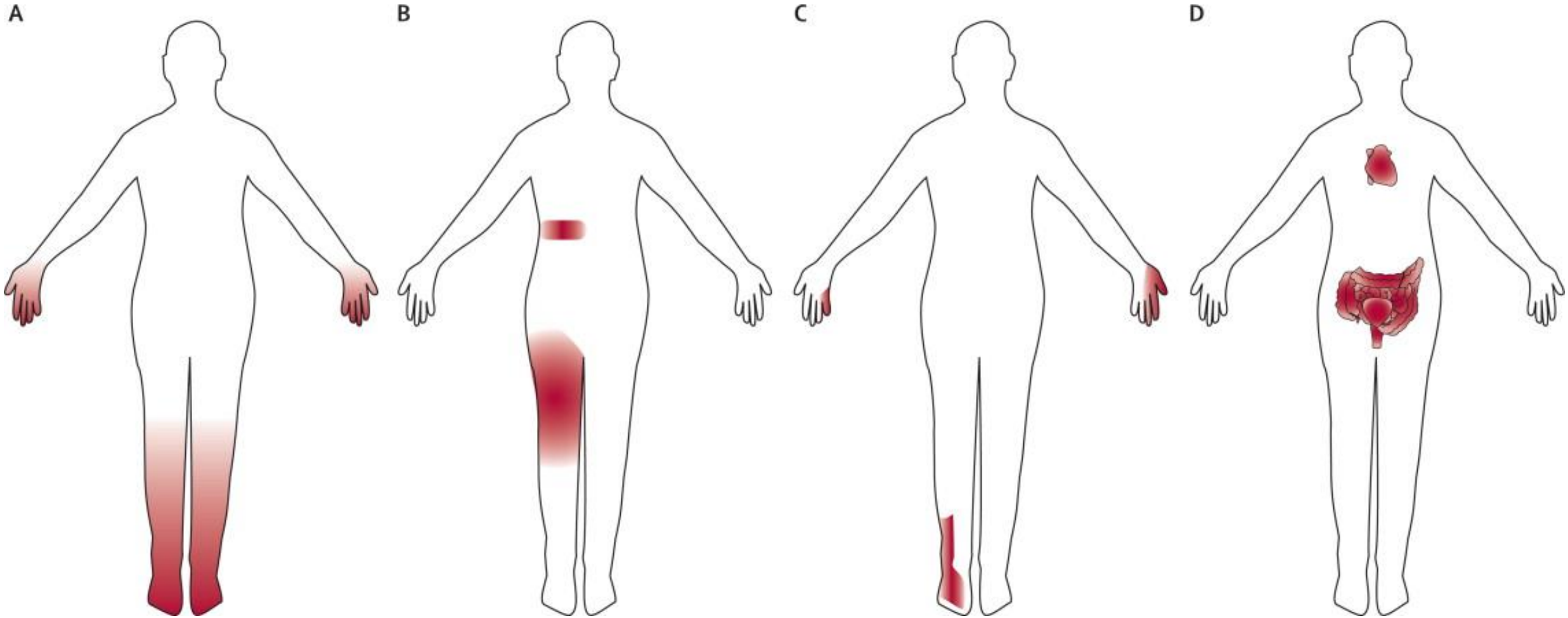
Distal sensory or sensorimotor polyneuropathy
Small-fiber neuropathy
Autonomic neuropathy
Large-fiber sensory neuropathy

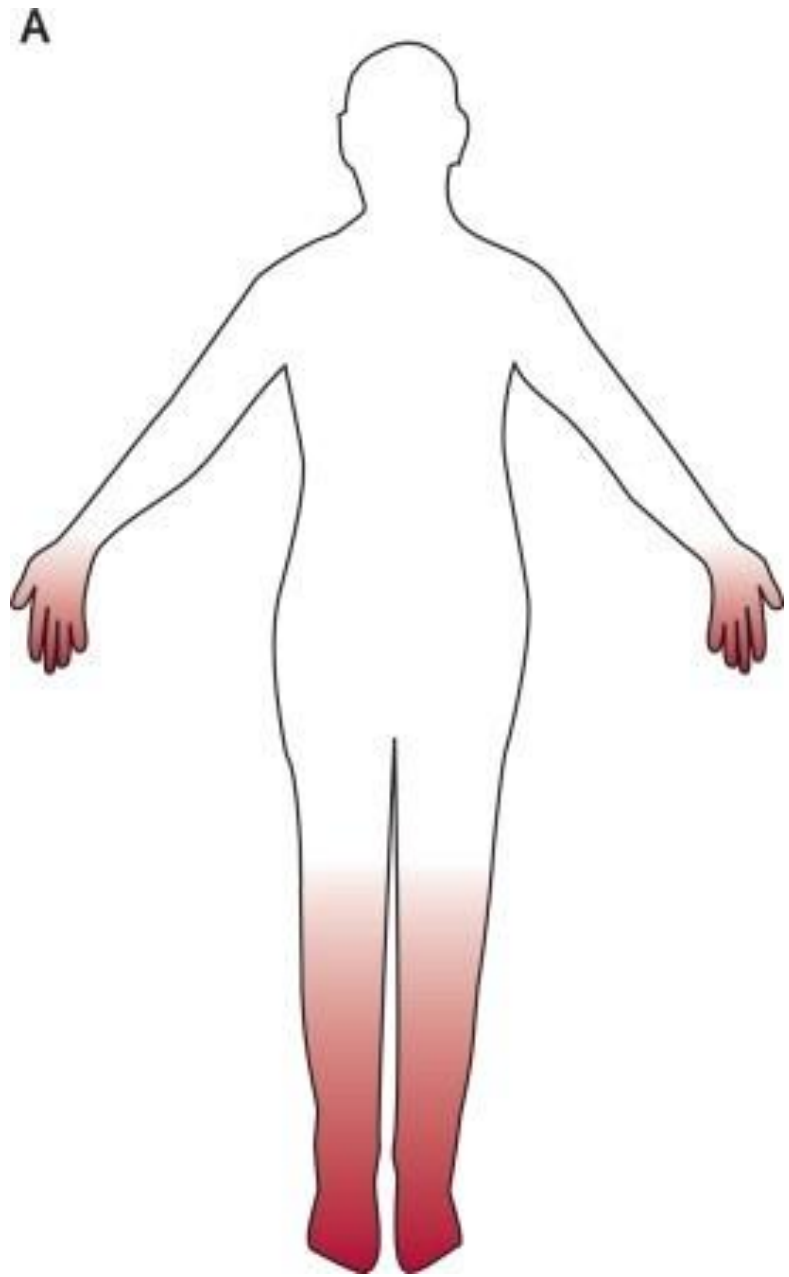
FOCAL AND ASYMMETRICAL NEUROPATHIES

Cranial neuropathy (single or multiple)
Truncal neuropathy (thoracic radiculopathy)
Limb mononeuropathy (single or multiple)
Lumbosacral radiculoplexopathy (amyotrophy, proximal neuropathy)

COMBINATIONS

Polyradiculoneuropathy
Diabetic neuropathic cachexia


A
B
C
D


A

DISTAL SYMMETRIC POLYNEUROPATHY

- The most common clinical presentation of neuropathy in diabetes.
- Accounting for roughly 50% to 75% of cases of diabetic neuropathy.
- DSPN may be subclassified further into two major subgroups, depending on the nerve fiber type most involved: large-fiber and small-fiber variants.
- Diabetic sensory neuropathy frequently forms a continuous spectrum ranging between these two polar types.
- Early DSPN in type 2 diabetes (or even prediabetes) preferentially involves small unmyelinated axons, frequently causing neuropathic pain, and gradually progresses to more involvement of large myelinated axons over time.

Small-fiber neuropathy

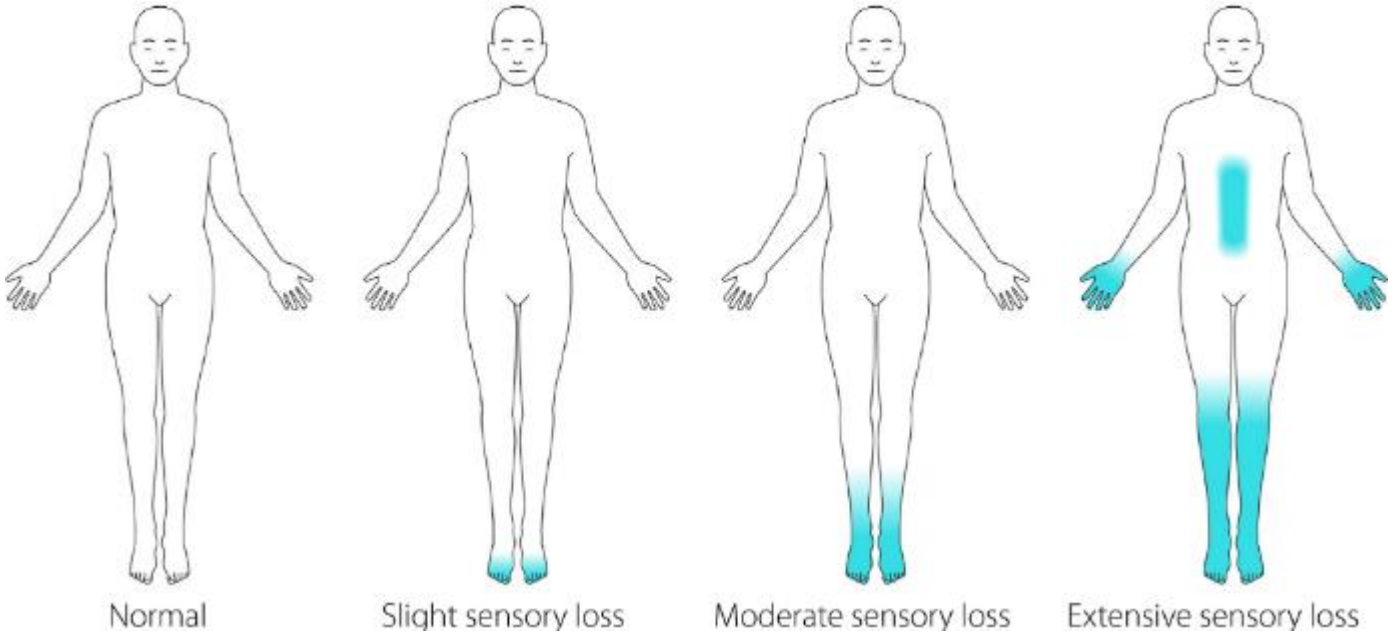
- Pain of a deep, burning, stinging, aching character, often associated with spontaneous shooting pains and allodynia to light touch.
- Pain and temperature modalities are impaired, with relative preservation of vibration and joint position sensation and muscle stretch reflexes.
- The small-fiber variant is often accompanied by autonomic neuropathy

Large-fiber neuropathy

- Large-fiber involvement is often asymptomatic, but sensory deficit may be detected by careful examination.
- The large-fiber neuropathy variant presents with painless paresthesia beginning at the toes and feet, impairment of vibration and joint position sense, and diminished muscle stretch reflexes.
- In advanced cases, significant ataxia may develop secondary to sensory deafferentation.

Distal Symmetrical Polyneuropathy

- Sensory deficits predominate.
- Sensory disturbances have a stocking-glove distribution following a length-dependent pattern.
- Most patients will develop only a minor motor involvement affecting the distal muscles of the lower extremities.
- Autonomic symptoms usually correlate with the severity of the neuropathy.



- Early sensory manifestations begin in the toes, gradually spreading proximally;
- When these reach above knee level, the fingers and hands become affected.
- In more advanced cases, sensation becomes impaired over the anterior chest and abdomen, producing a truncal wedge-shaped area of sensory loss.

Diagnosis

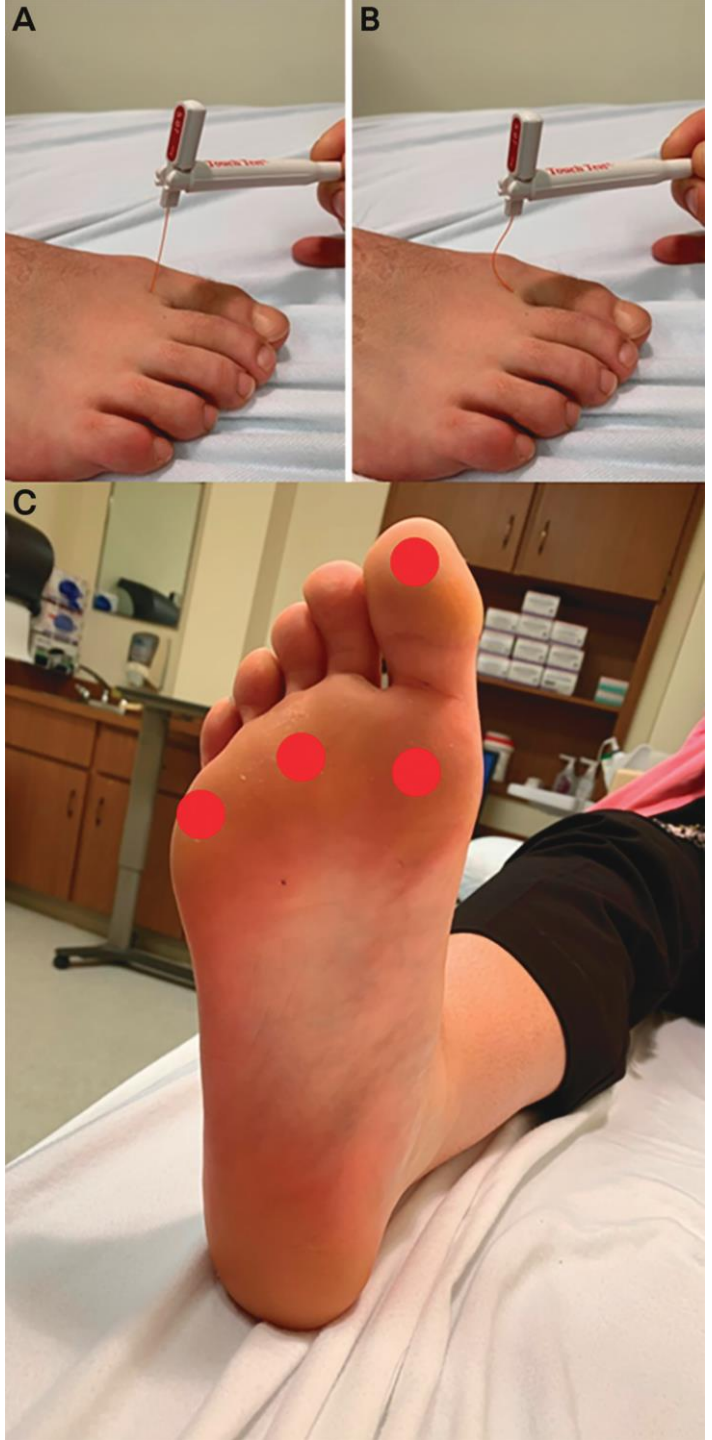
- The diagnosis of DSPN in diabetes is based on history, clinical examination findings, and nerve conduction studies in select cases.
- The appropriate clinical evaluation for DSPN includes, but is not limited to, examination of muscle strength, deep tendon reflexes, and sensation (vibration, proprioception, thermal, pain, and light touch sensation).
- The presence of atypical features such as significant asymmetry, an acute onset, or early motor involvement suggests a different neuropathy type or diagnosis and should prompt further diagnostic evaluation, including nerve conduction studies and EMG.
- Although DSPN is generally symmetric (by definition), symptoms may initially be reported in one limb and then gradually evolve into a symmetric pattern over time.

Diagnosis

- However, a significant asymmetry on neurologic examination is unusual and should prompt additional testing.
- Some patients present with pain in the distribution of the neuropathy (approximately 25% to 35%), whereas other patients are asymptomatic.
- Patients with neuropathic pain in the setting of DSPN typically present much earlier in the disease course than those without pain.

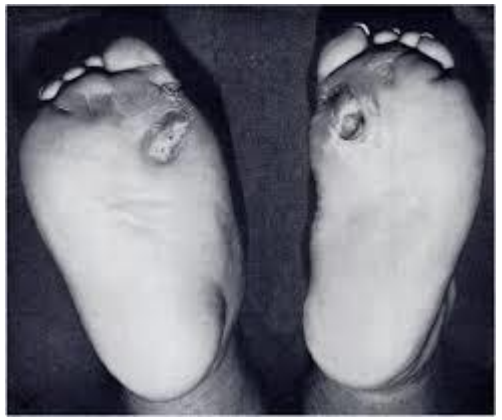
Pressure perception

- 10-gram monofilament
- Those unable to detect 7 of 10 applications are at significantly elevated risk for painless injury and should be referred for appropriate podiatric foot care.



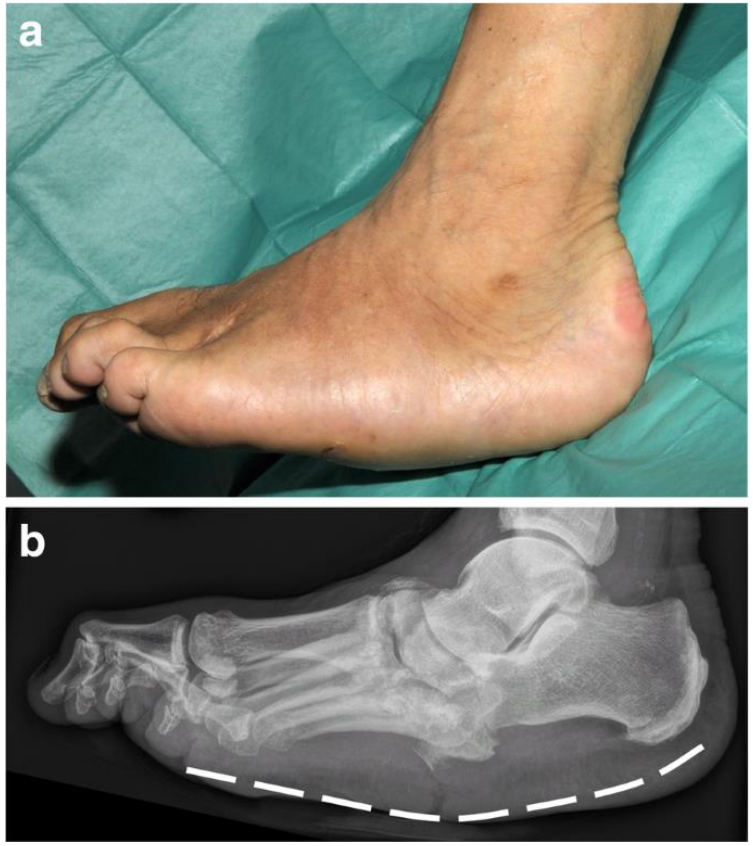
Acrodystrophic neuropathy

- Sensory loss makes patients with diabetes susceptible to repetitive, often unnoticed injuries that set the stage for foot ulcers and distal joint destruction.
- Chronic foot ulceration is one of the more severe complications of diabetes mellitus, occurring in 4% to 10% of patients, and is due to a combination of unnoticed traumatic tissue damage, vascular insufficiency, and secondary infection.
- Prevention is better than treatment.
- Daily inspection and proper foot care can prevent or lessen the severity of this complication.



Neuropathic arthropathy

- Charcot joint formation.
- Is a complication seen in patients with diabetes who often have foot ulcers and autonomic impairment.
- Tends to involve the small joints in the feet.
- The role of pronounced inflammatory reactions and cytokines following the initial joint insult resulting in increased osteoclastogenesis has recently been emphasized
- The abundance of osteoclasts causes progressive bone loss, leading to further fractures and potentiation of inflammation and osteoclast formation.



Management

- No disease-modifying therapies.
- Education about the underlying problem.
- Treatment of modifiable risk factors.
- To improve glycemic control.
- To more aggressively manage lipids and blood pressure.
- To counsel on tobacco cessation.
- Advocating for an increase in exercise.
- Should be counseled on foot care.
- Should always wear hard-soled shoes.
- Should make sure to check their feet at least once daily.
- Should have a very low threshold for seeking medical attention in the setting of a foot injury.

NEUROPATHY ASSOCIATED WITH METABOLIC SYNDROME AND PREDIABETES

- Prediabetes (impaired fasting glucose or impaired glucose tolerance) may precede the diagnosis of type 2 diabetes by several years.
- A hemoglobin A1c level of 5.7% to 6.4%.
- The prevalence of neuropathy in prediabetes is approximately 10%.
- Symptoms, EDX abnormalities, and intraepidermal nerve fiber density reduction consistent with a predominantly small-fiber neuropathy that may be either painful or painless.
- Although with changes less pronounced than in their diabetic counterparts.
- A growing body of literature links metabolic syndrome with DSPN risk.

Impaired glucose tolerance neuropathy

- A smaller number of patients may present with autonomic dysfunction, primarily manifesting as reduced cardiovagal function with a resting tachycardia and reduced exercise tolerance.
- Among individuals with otherwise “idiopathic” neuropathy, the presence of prediabetes is approximately 25%.
- The implication for clinical practice is that patients with undiagnosed painful peripheral neuropathy should undergo OGTT.
- Early diagnosis followed by improved lifestyle may result in reversal of impaired glucose tolerance and neuropathy.

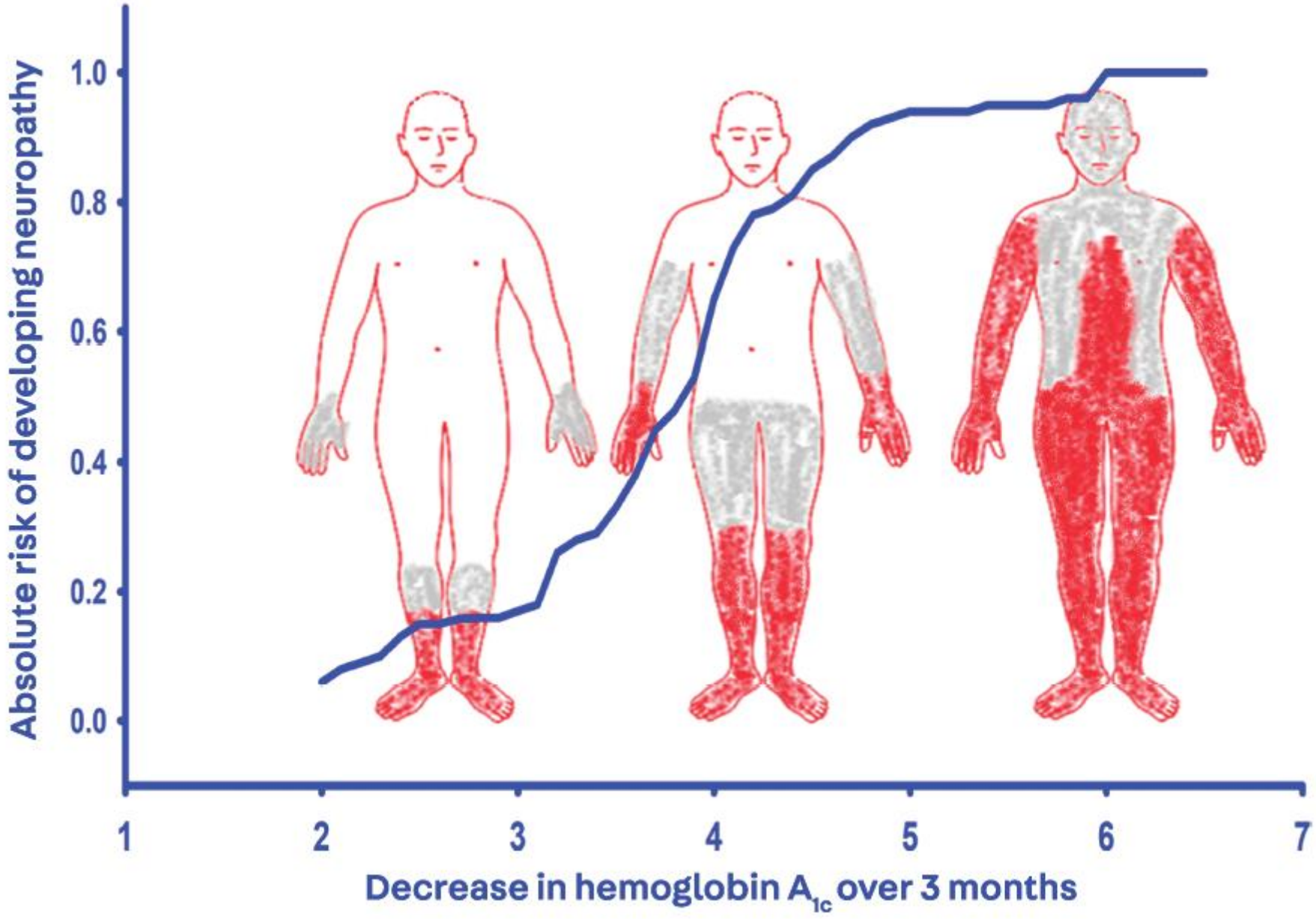
Treatment-Induced Neuropathy of Diabetes

- Previously known as insulin neuritis, or acute painful neuropathy.
- Develops suddenly following rapid improvement in glycemic control in the setting of chronic hyperglycemia.
- Most commonly seen after a significant treatment change in individuals with type 1 diabetes who have had chronic hyperglycemia or in individuals with newly discovered type 2 diabetes with an unknown period of hyperglycemia combined with an aggressive lowering of the hemoglobin A_{1c}.
- The neuropathy predominantly involves small fiber sensory and autonomic nerve fibers
- characterized by the acute onset of neuropathic pain in a length-dependent or generalized distribution, often with accompanying autonomic symptoms.

Treatment-Induced Neuropathy of Diabetes

- Symptoms typically begin 2 to 6 weeks after the change in glucose control.
- Pain persists for weeks or up to several months, with spontaneous resolution to follow.
- Autonomic symptoms are sometimes prominent, including orthostatic intolerance or hypotension, hyperhidrosis or anhidrosis, early satiety, and erectile dysfunction, but they are frequently overlooked given the severity of the neuropathic pain.
- The severity of neuropathy in treatment-induced neuropathy of diabetes is tied to the magnitude and rate of the change in hemoglobin A_{1c}.

- Individuals with the largest changes in glucose control have the largest region of body involvement, the most severe pain, and the greatest symptoms of autonomic dysfunction.



Treatment-Induced Neuropathy of Diabetes

- Pathological studies demonstrate active axonal regeneration, which may act as generators of spontaneous nerve impulses.
- In addition to the development of neuropathy, individuals who develop treatment-induced neuropathy of diabetes also frequently have renal and retinal involvement simultaneously,
- The majority of individuals with treatment-induced neuropathy of diabetes have significant progression of proliferative retinopathy over a period of 12 months.
- Renal function may decline, although increased microalbuminuria is the most common manifestation.

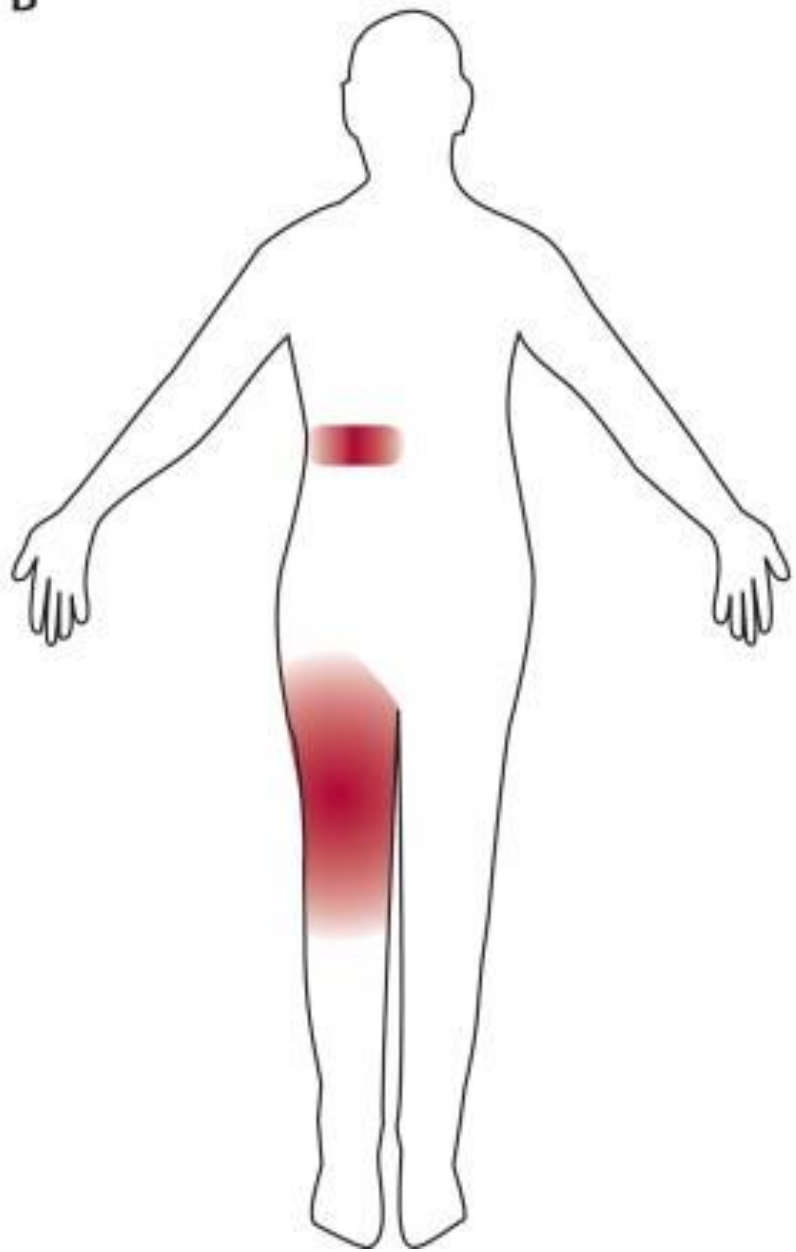
Treatment-Induced Neuropathy of Diabetes

- Managing symptomatic pain
- Encouraging glucose stabilization at the current hemoglobin A1c level until symptoms begin to improve.
- Avoiding dramatic improvements in hemoglobin A1clevels in individuals with chronic hyperglycemia is recommended (limiting change to 1% reduction in the hemoglobin A1c per month).

Diabetic neuropathic cachexia

- An acute and severe painful diabetic neuropathy associated with precipitous severe weight loss, depression, insomnia, and impotence in men.
- The syndrome is more common in men with poor glucose control. Improved glucose control and weight gain often result in recovery and improvement of EDX abnormalities.
- The reason for profound weight loss, severe pain, and spontaneous recovery remains obscure.

B



Diabetic Lumbosacral Radiculoplexus Neuropathy

- Different presentations of the same basic involvement of multiple nerve roots or proximal nerve segments. : Diabetic amyotrophy, thoracolumbar radiculopathy, and proximal or diffuse lower extremity weakness.
- The incidence to be approximately 4.2 per 100,000 per year.
- Most common in middle-aged (older than 50 years) patients with type 2 diabetes.
- Is more common in men than in women.
- The disorder is rare in young adults or children.
- The onset is unrelated to the duration of diabetes, and the condition may develop in patients with long-standing NIDDM during periods of poor metabolic control and weight loss, but it can also occur in mild and well-controlled diabetics or be the presenting feature of diabetes.
- Pathologic data suggest it is caused by a microvasculitis resulting in ischemic nerve injury.

Diabetic Lumbosacral Radiculoplexus Neuropathy

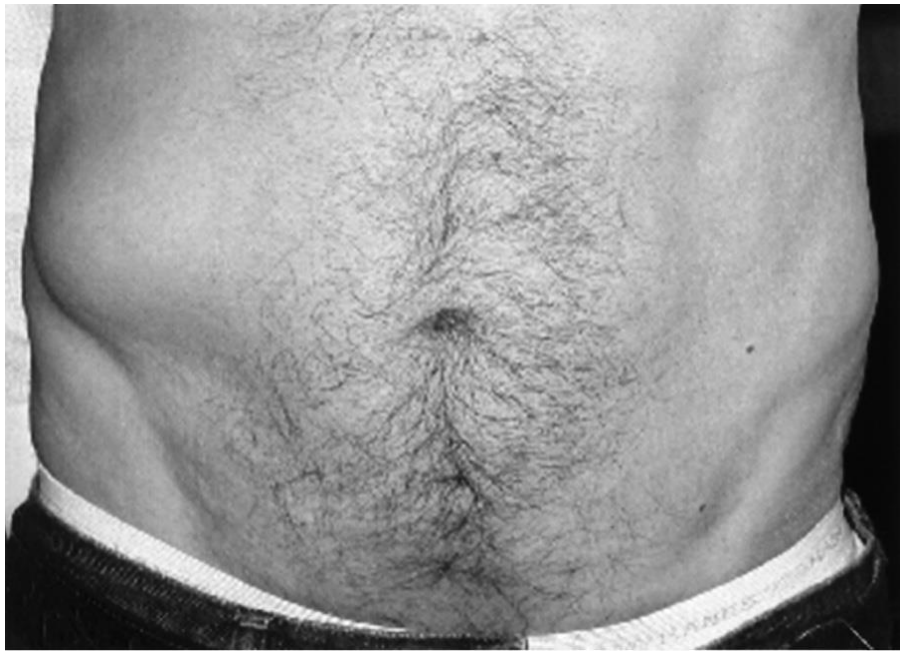
- Typically, unilateral severe pain in the lower back, hip, and anterior thigh heralds the onset of neuropathy.
- Within days to weeks asymmetrical weakness ensues, affecting proximal and, to a lesser extent, distal lower-extremity muscles (iliopsoas, gluteus, thigh adductor, quadriceps, hamstring, and anterior tibialis).
- Reduction or absence of knee and ankle jerks is the rule. Numbness or paresthesias are minor complaints.
- In some cases, the opposite leg becomes affected after a latency.
- Weight loss occurs in more than half of patients
- The progression may be steady or stepwise and may continue for many months (in some cases as long as 18months).

Diabetic Lumbosacral Radiculoplexus Neuropathy

- Pain usually recedes spontaneously long before motor strength begins to improve.
- Most patients require assistance with ambulation and aggressive pain management.
- Recovery takes up to 24 months because of the slow rate of axonal regeneration. In many cases, mild to moderate weakness persists indefinitely.
- Less commonly, patients may present with a symmetric motor-only form.
- Although a beneficial effect of immunomodulating therapies has been proposed, controlled studies have shown no positive effect for corticosteroids in enhancing the recovery of the motor deficit.
- A small randomized trial suggested that IV methylprednisolone may help neuropathic pain associated with diabetic lumbosacral radiculoplexus neuropathy.

Diabetic Truncal Neuropathy (thoracic radiculopathy)

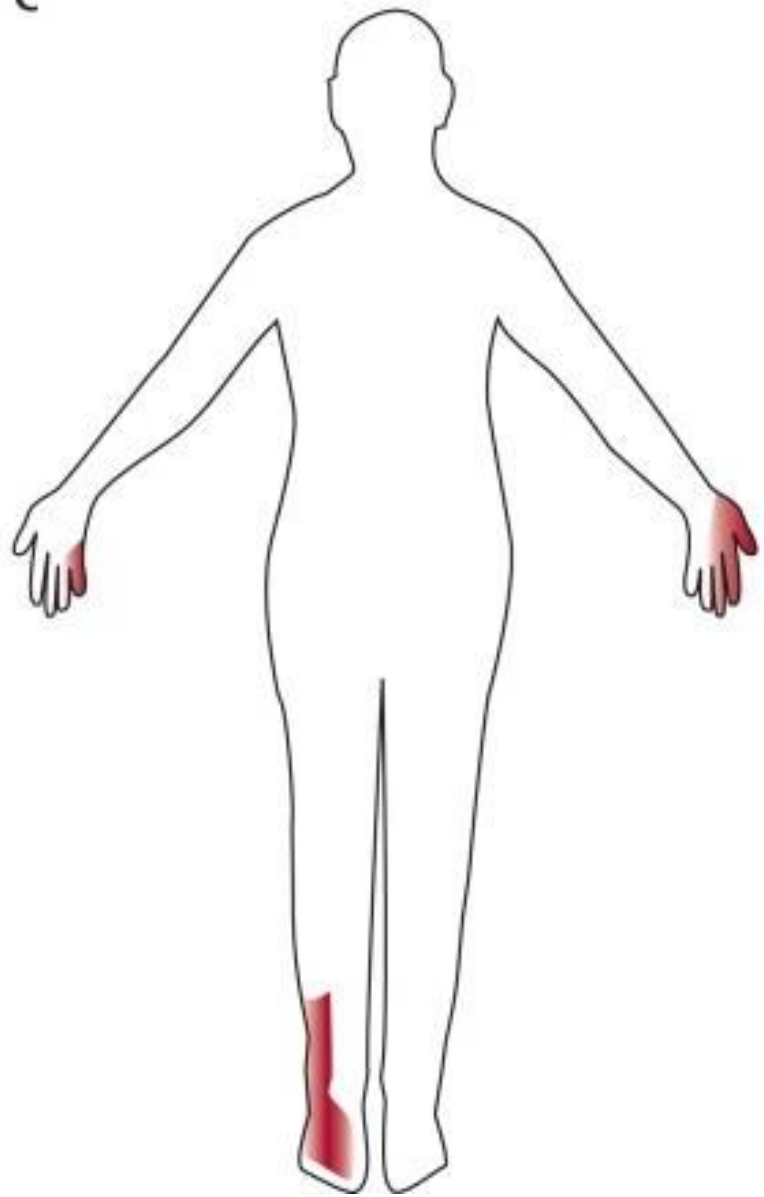
- Involving the T4 through T12 spinal nerve roots causes pain or dysesthesias in areas of the chest or abdomen, thereby producing diagnostic confusion.
- Bulging of the abdominal wall as a result of weakness of abdominal muscles may also occur.



Diabetic Truncal Neuropathy (thoracic radiculopathy)

- This unique truncal pain is seen in older patients with NIDDM.
- May occur either in isolation or together with the typical lumbosacral radiculoplexopathy.
- Patients describe burning, stabbing, boring, beltlike pain.
- Contact with clothing can be very unpleasant.
- The onset may be either abrupt or gradual.
- In some patients preceded or accompanied by a profound weight loss.
- Neurological findings are limited to hypoesthesia or hyperpathia over the thorax or abdomen.
- The symptoms may persist for several months before gradual and spontaneous resolution within 4 to 6 months.

C



Limb Mononeuropathy

- Caused by two basic mechanisms: nerve infarction or entrapment.
- Mononeuropathy secondary to nerve infarction has a stereotyped presentation, with abrupt onset of pain followed by variable weakness and atrophy.
- Mononeuropathies due to nerve entrapment are more common than nerve infarctions.
- Entrapment neuropathies, including median mononeuropathy at the wrist (carpal tunnel syndrome), ulnar mononeuropathy at the elbow (cubital tunnel syndrome), and fibular (peroneal)mononeuropathy at the fibular head are more prevalent in individuals with diabetes when compared to the general population.

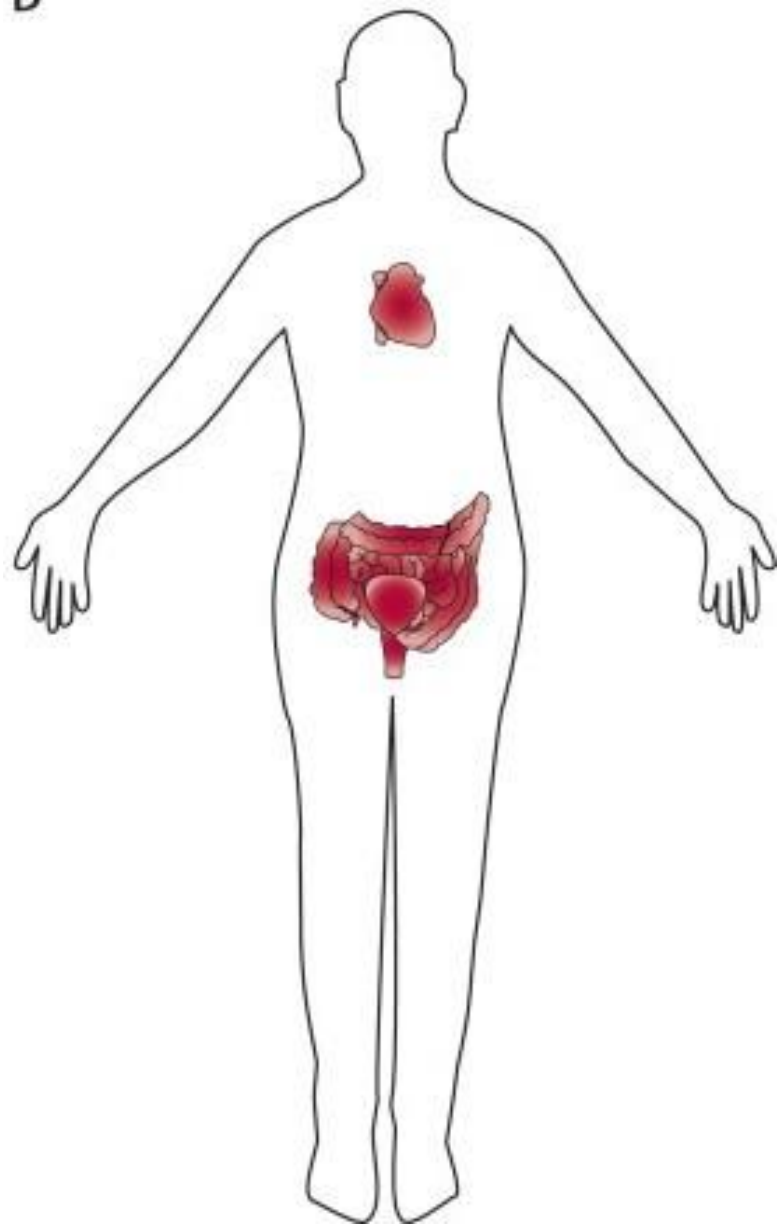
Limb Mononeuropathy

- Diabetes mellitus is a risk factor for single or multiple entrapment neuropathies.
- Diabetes is found in 8% to 12% of patients presenting with CTS.
- The risk for CTS is more than twofold for patients with diabetes than in the general population.

Cranial Mononeuropathies

- A third-nerve palsy is the most commonly encountered diabetic cranial mononeuropathy.
- Pupillary sparing, the hallmark of diabetic third-nerve palsy, results from ischemic infarction of the centrifascicular oculomotor axons due to diabetic vasculopathy of the vasa nervorum.
- With decreasing frequency, the fourth, sixth, and seventh nerves are also affected.

D



Autonomic Neuropathy

- Diverse spectrum of clinical manifestations because of the different organ systems involved.
- Usually correlates with the severity of somatic neuropathy.
- The spectrum of autonomic involvement ranges from subclinical functional impairment of cardiovascular reflexes and sudomotor function to severe cardiovascular, gastrointestinal, or genitourinary autonomic dysfunction.
- Orthostatic hypotension, resting tachycardia, or diminished heart-rate response to respiration are the hallmarks of diabetic cardiac autonomic neuropathy.
- An increased incidence of painless or silent myocardial infarction is reported in diabetic patients with autonomic neuropathy.
- It is important to investigate the cardiac autonomic neuropathy of diabetes by appropriate noninvasive autonomic function tests, because the presence of such autonomic dysfunction predicts cardiovascular morbidity and mortality.

Diabetic Cardiovascular Autonomic Neuropathy

- It is associated with a significant increase in both morbidity and mortality.
- may range from an increased resting heart rate to diminished heart rate response to physiologic stress.
- As cardiovascular autonomic neuropathy becomes more severe, orthostatic hypotension (defined as a fall in blood pressure of >20mmHg systolic and 10 mm Hg diastolic) develops, which is the most severe and debilitating form of cardiovascular autonomic neuropathy.
- The end result of cardiovascular autonomic neuropathy is diminished cardiac output, particularly in association with exercise.

Diabetic Cardiovascular Autonomic Neuropathy

- Patients with diabetes who have orthostatic hypotension in the setting of cardiovascular autonomic neuropathy have a 5- to 10-year mortality range between 27% and 56%.
- At present, no treatment exists for the underlying disease.
- No evidence has shown that symptomatic therapy reduces the associated morbidity and mortality.
- As a consequence, the primary goal is prevention of disease development and progression with glycemic control and aggressive management of other features of metabolic syndrome.

GASTROPARESIS

- Causes delayed transit of food (solids or liquids) from the stomach into the small intestine.
- It is present in up to 50% of individuals with diabetes.
- Many patients report postprandial fullness, nausea, bloating, or vomiting, although some patients may be asymptomatic.
- It further complicates glycemic control by causing a mismatch between glucose absorption and administration of insulin.
- Objective assessment of gastroparesis severity is recommended.
- A separate and potentially reversible component is directly related to hyperglycemia.

Treatments

- Having patients eat smaller, more frequent meals (this strategy can further complicate glycemic control)
- Avoiding dietary fiber and fat is recommended.
- Removal of any offending medications (such as opioids, clonidine, tricyclic antidepressants, calcium channel blockers, dopamine agonists, muscarinic cholinergic receptor antagonists, glucagonlike peptide 1 [GLP-1] agonists, phenothiazines, and cyclosporine)
- Metoclopramide (duration of therapy beyond 5 days is not recommended)

CONSTIPATION.

- Up to 60% of patients affected.
- The patient's medication list should be closely investigated.
- Constipation due to colonic hypomotility is more common than diarrhea.

DIARRHEA

- It is typically a profuse and watery diarrhea that usually presents during sleep.
- It is more common in individuals with type 1 diabetes
- often associated with fecal incontinence.
- Associated weight loss or malabsorption is rare.
- Reported in up to 20% of individuals with diabetes.
- It may alternate with constipation or may persist as diarrhea for hours at a time.
- loperamide, codeine, combination diphenoxylate and atropine, or tincture of opium.

BLADDER DYSFUNCTION

- Reported in up to 50% of individuals with diabetes.
- The symptoms of urinary autonomic dysfunction develop insidiously and progress slowly.
- One of the initial symptoms of autonomic neuropathy involving the bladder is impaired sensation of fullness.
- As neuropathy severity increases, bladder atony leads to prolonged intervals between voiding, gradually increasing urinary retention, and finally overflow incontinence.
- Patients with diabetes who have neurogenic bladder should be encouraged to void routinely every few hours to prevent urinary retention.
- Medications that impair detrusor activity include anticholinergic agents, tricyclic antidepressants, and calcium channel antagonists.

Sudomotor Function

- Necessary for proper homeostatic thermoregulation as well as skin health.
- May present as the earliest clinical manifestation of neuropathy.
- Sudomotor abnormalities result in distal anhidrosis, typically presenting in a stocking-and-glove distribution.
- Interestingly, patients do not present with symptoms related to distal anhidrosis but instead report proximal hyperhidrosis to maintain thermoregulation.
- Patients feel that they are sweating too much over their head and trunk.
- Another classic finding in diabetic neuropathy, although less common than distal anhidrosis, is gustatory sweating. Sweat will appear over the face, head, neck, shoulders, and chest after eating.
- Oral or topical glycopyrrolate may prove partially effective in some patients.

Conclusion

- Unfortunately, once the diabetic neuropathy is established, the existing damage is largely irreversible
- The cornerstone in the treatment of diabetes and its complications remains optimal glucose control.
- Good diabetic control is associated with less frequent and less severe peripheral nerve complications.