

Diabetic polyneuropathy

Risk factors, patterns of presentation, diagnosis, and treatment

Ann Noelle Poncelet, MD

Diabetic symmetrical distal neuropathy or diabetic polyneuropathy is the most common form of diabetic neuropathy and a leading cause of neuropathy in the United States. Complications include pain, loss of ambulation, and risk for amputation. Recognizing the typical pattern of presentation and risk factors for diabetic polyneuropathy is essential for making the correct diagnosis and determining appropriate workup and need for neurologic consultation. Intensive glucose control is the only therapy proven to prevent or slow the progression of diabetic polyneuropathy. Supportive therapies, including pain management and podiatric care, can improve quality of life and prevent chronic ulcerations.

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Diabetes mellitus is one of the most common causes of neuropathy.¹ Diabetic polyneuropathy results in significant disability and morbidity including severe pain, loss of ambulation, and an increased risk of non-healing ulcers and amputation.²⁻⁴ Appropriate diagnosis of diabetic polyneuropathy, exclusion of other treatable causes, and treatment are important to prevent secondary complications and improve quality of life.

Various types of diabetic neuropathy

have been described.^{5,6} A hyperglycemic neuropathy in patients who are newly diagnosed or poorly controlled may occur with uncomfortable distal sensory symptoms; these symptoms resolve rapidly when blood glucose is brought under control. Symmetric neuropathies include sensory and/or autonomic neuropathy and acute painful neuropathy. Focal neuropathies such as cranial neuropathy, thoraco-abdominal neuropathy, focal limb neuropathies (median, ulnar, and femoral) and diabetic amyotrophy can also occur, as well as a combination of the various types of neuropathies in the same patient. This review will focus on the most common form, diabetic symmetrical distal neuropathy (diabetic polyneuropathy). Tables include disabilities and symptoms and pharmacologic management options.

Epidemiology

The incidence of diabetic polyneu-

ropathy in patients with diabetes ranges from 10 to 50%.² Approximately 10% of patients have neuropathy at the time diabetes is diagnosed and more than one-half of adults with diabetes have neuropathy after 25 years.^{5,7} The incidence is similar, regardless of type of diabetes.⁵ New data on the rate of development of clinically significant neuropathy in type 1 diabetes patients with the advent of improved glucose control may become available through a 10-year observational study of the Diabetes Control and Complications Trial cohort.⁸ The UK Prospective Diabetes Study (UKPDS) included a prospective 10-year observational study of the association of hyperglycemia and microvascular complications of type 2 diabetes.⁹ There was a 37% decrease in microvascular endpoints observed per 1% reduction in glycosylated hemoglobin. Results for neuropathy endpoints were not reported.

The severity of the neuropathy is related to the duration of the disease, age, metabolic control, the presence of hypertension, and hyperlipidemia.¹⁰ Chronic neuropathic pain is present in 20% of patients with a >10 year history of diabetes.¹¹ Neuropathy is an independent risk factor for foot ulceration and amputation,^{4,12} and patients with diabetic polyneuropathy have a 15% chance of amputation in their lifetime.⁷ The lifetime risk of amputation in all patients with diabetes is 5 to 15%.¹³ Potter et al found evidence of neuropathy in the contralateral limb

Dr. Poncelet is an associate clinical professor in the department of neurology at the University of California in San Francisco.

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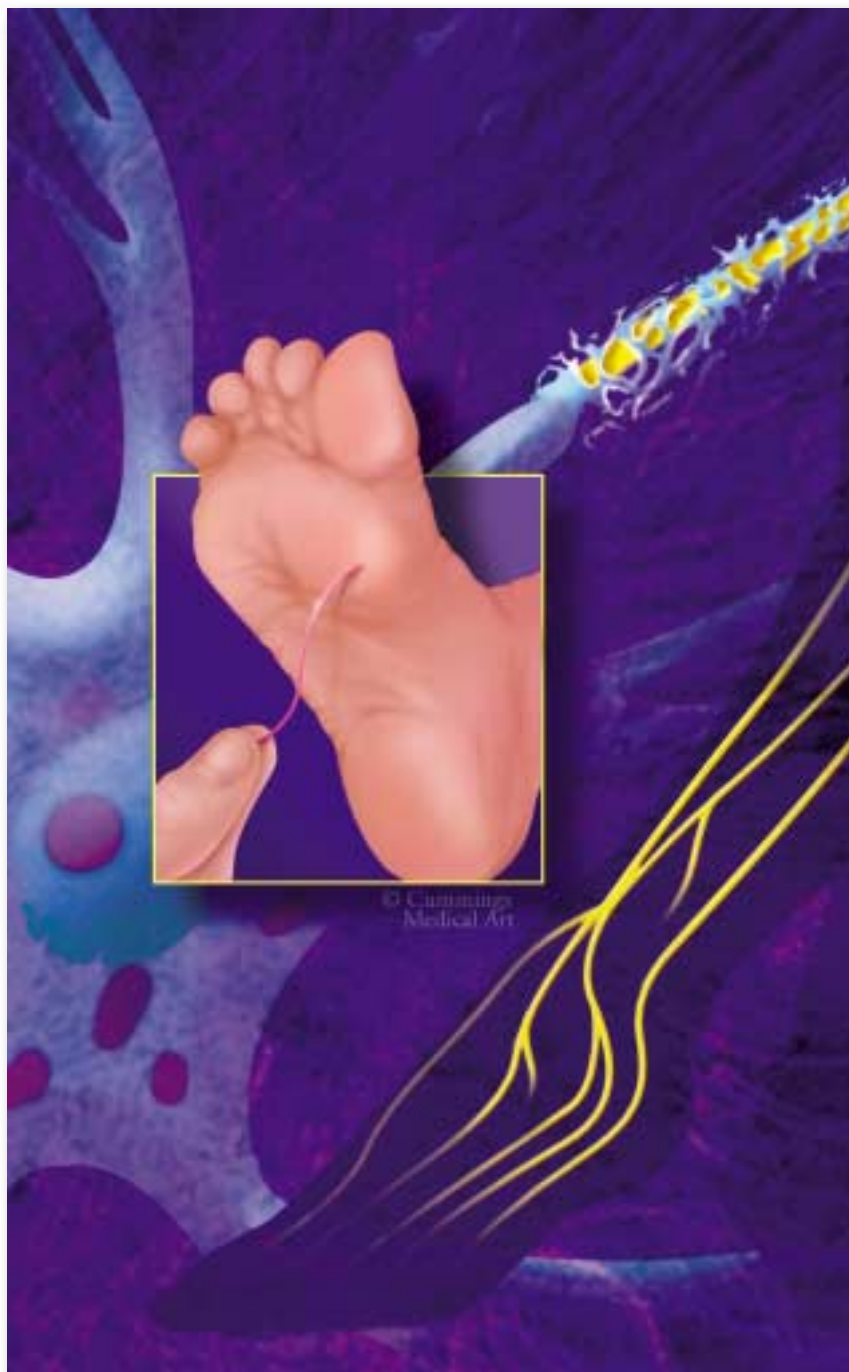
of 97% of diabetic patients at the time of amputation.¹²

Clinical features

The pathogenesis of diabetic polyneuropathy is not completely understood. However, there is general agreement that the root cause is excess glucose.^{7,14} Diabetic polyneuropathy presents in the distal lower extremities. The small unmyelinated fibers may initially be affected with loss of the ability to sense painful stimuli, loss of temperature sensation, and neuropathic pain.¹⁵ The characteristic symptoms of neuropathic pain include burning, shooting or lancinating pain, allodynia (pain due to a stimulus that does not normally provoke pain), paresthesias (sensations or tingling that are not provoked by any stimulus) and hyperesthesia (sensation in response to a stimulus that is greater than the normal response but not painful), aching, cramping, and nocturnal exacerbation.¹¹ Patients can also present with large fiber sensory abnormalities including loss of sensation and imbalance due to proprioceptive loss.¹⁵

The natural history of diabetic neuropathy is relentless progression with involvement of both large and small fiber modalities and spread of the symptoms in a sock-like distribution proximally. When the symptoms reach the level of the knees, similar symptoms begin at the fingertips and gradually spread up the arms. Motor involvement occurs later with distal loss of strength. In a given patient, the rate of progression depends on total hyperglycemic exposure, age, the presence of hypertension and hyperlipidemia.^{10,16} Painful symptoms may remit with progression of the neuropathy.¹¹ Functional disabilities and autonomic symptoms are listed in Table 1.

The neurologic examination shows a loss of light touch, pinprick, and temperature in a distal pattern resembling the outline of socks in the legs and gloves in the hands (stocking/glove distribution). Vibration and position sense are reduced distally and when more severe, a Romberg may be positive. A pos-



itive Romberg occurs when the patient, whose feet are together and eyes are closed, falls backwards. The motor examination is normal early in the neuropathy, but later may show distal atrophy in the lower extremities. Direct strength testing of toe flexion should be

Illustration for Geriatrics by Sally Cummings

included in the neurologic examination, as toe flexor weakness usually occurs first. The loss or reduction in deep tendon reflexes parallels the sensory loss. Prominent upper extremity involvement is often due to superimposed compressive neuropathies (eg, carpal tunnel syn-

Dr. Cummings is a geriatrician at the University of Michigan Medical Center, Ann Arbor, Michigan.

Table 1 Functional disabilities and autonomic symptoms due to diabetic polyneuropathy

Functional disabilities	Autonomic symptoms
Impaired gait	Urinary hesitancy and incontinence
Proprioceptive loss	Impotence
Pain	Abnormal sweating
Weakness	Heart rate abnormalities
Impaired fine finger movements	Postural hypotension
Sensory loss	Gastric bloating
Pain	Diarrhea
Weakness	Constipation

Source: Prepared for Geriatrics by Ann Noelle Poncelet, MD.

drome, ulnar neuropathy at the elbow, or both) or a non-diabetic etiology (eg, Guillain Barre syndrome, porphyria, hereditary sensorimotor neuropathy, hereditary motor neuropathies, vitamin B₁₂ deficiency, vasculitic neuropathy, paraneoplastic neuropathy). Sensory neuropathy is a major initiating factor in the development of foot ulceration and infection with the possibility of amputation. A mutilating arthropathy can occur with more severe neuropathy—approximately 10% of patients with di-

Diabetic patients need an annual neurologic and clinical evaluation of the foot

abetic polyneuropathy develop Charcot joints.² The most frequent location is the tarsal-metatarsal region. There is often a history of a minor trauma, followed by a hot, swollen joint that is painful in up to one-third of cases. Progressive destruction over several months results in a Charcot joint with displacement and subluxation of the tarsus downward (rocker bottom deformity) and/or a medial convexity from displacement of the talonavicular joint or from tarsometatarsal dislocation.

Patient assessment

Diabetic polyneuropathy is diagnosed on the basis of distal symmetrical sensory symptoms and a focused neurologic examination confirming sensory, motor, and reflex findings in a distal symmetrical pattern. The American Diabetes Association (ADA) recommends that all patients with diabetes receive an annual neurologic evaluation and a careful clinical evaluation of the foot.¹⁷ The latter includes assessment of vascular status, foot structure and biomechanics, and skin integrity. ADA also recommends that people with neuropathy have a visual inspection of their feet at every visit with a health care professional. Abnormal screening results should signal full diagnostic workup, including a careful history to exclude other causes of neuropathy (eg, alcohol history, prescription drugs, diet, use of supplements, toxic exposures, and family history). The workup should also include a complete neurologic examination, electromyography (EMG)/nerve conduction studies as well as laboratory studies to exclude other treatable causes of neuropathy such as renal failure, B₁₂ deficiency, and hypothyroidism.¹⁸ A laboratory screen for distal symmetrical sensorimotor neuropathy in non-diabetic patients includes fasting serum glucose, glycosylated hemoglobin, blood urea nitrogen, creatinine, complete blood count, erythrocyte sedimentation rate, urinalysis, vitamin B₁₂ level, and thyrotropin stimulating hormone levels.¹⁸ Patients with diabetic polyneu-

ropathy should also be screened for diabetic retinopathy and nephropathy.

Differential diagnosis

Although diabetes is a common cause of neuropathy, it is important not to assume that a neuropathy in the context of diabetes is due to diabetes. Approximately 1 out of 100 patients with a neuropathy from non-diabetic causes will also have diabetes. Features that raise suspicion of other etiologies include:

- neuropathy which develops prior to or early in the course of the diabetes,
- neuropathy in the context of well-controlled diabetes,
- asymmetrical involvement,
- significant proximal involvement or upper extremity involvement.

Diabetic polyneuropathy usually occurs in the context of other secondary diabetes complications including nephropathy and retinopathy. The above unusual features should prompt neurologic evaluation with referral to a neurologist and EMG/nerve conduction studies. Even patients with typical features should be screened for treatable causes of neuropathy, such as B₁₂ deficiency and hypothyroidism.

Treatment

There is no cure for diabetic neuropathy, but it is treatable. Preventive steps are essential to avoid diabetic foot ulcers, including visual inspection and routine podiatric care. The only treatment proven to slow and even improve the progression of diabetic neuropathy is intensive glycemic control in patients with insulin-dependent diabetes.^{19,20} (Intensive treatment is typically defined as 3 or more daily insulin injections or continuous subcutaneous insulin infusion [insulin pump]; HbA_{1c} values are kept between 6.5 and 7.5.) The Diabetes Control and Complications Trial (DCCT) was a multicenter, randomized clinical trial of intensive versus conventional treatment on the incidence and progression of retinopathy in 1,441 insulin-dependent diabetic subjects (mean age, 27; range 13 to 39) who were followed for 3 to 9 years (mean 6.5).

continued

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Table 2 Pharmacologic management of neuropathic pain in older adults*

Drug	Dosage	Comments [†]
Antidepressants		
Amitriptyline HCl	10 to 50 mg PO qhs gradually increase by 10 mg every 4 to 7 days	Monitor for cardiac abnormalities; do not use with monoamine oxidase inhibitors (MAOIs); may increase risk of falls, blood glucose swings, confusion.
Nortriptyline HCl	10 to 100 mg PO qhs	
Desipramine HCl	10 to 100 mg PO qhs	
Imipramine HCl	10 to 100 mg PO qhs	
Paroxetine HCl	10 to 60 mg PO qd	
Anticonvulsants		
Gabapentin	300 to 1200 mg PO tid start at 100 mg PO tid	Sedation
Phenytoin	200 to 400 mg PO qhs	Monitor for gait impairment, toxicity by free dilantin levels; use with caution in patients with hypotension or hyperglycemia.
Carbamazepine	200 to 400 mg PO bid	Black box warning for aplastic anemia and agranulocytosis; monitor for blood counts and liver function.
Valproate sodium	250 mg PO tid start 250 mg PO qd	Black box warning for hepatic failure; monitor blood levels.
Analgesics		
NSAIDs		Use caution in patients with risk factors for GI bleeds; refrain from long-term use.
Tramadol HCl	50 to 100 mg PO q 4 to 6 hours prn; maximum dose 300 mg/d	
Antiarrhythmics		
Lidocaine 5% patch	apply up to 12 hours/day	Use with caution in patients receiving Class I antiarrhythmic drugs.
Mexiletine HCl	150 mg/d for 3 days, then 300 mg/d for 3 days followed by 10 mg/kg/d	May worsen arrhythmias.
Topical		
Capsaicin 0.075% cream	Apply to affected area tid/qid	

*Efficacy has been shown for painful diabetic neuropathy in randomized controlled trials with the exception of NSAIDs.¹¹

[†] Before prescribing any agent, check for possible Black box warnings, investigate possible drug-drug interactions, review potential adverse events, and verify dosing recommendations.

Source: Created for Geriatrics by Ann Noelle Poncelet, MD.

The incidence and progression of neuropathy, nephropathy, and cardiovascular disease were secondary endpoints. The rate of clinical neuropathy at 5 years was 9.8/100 patient-years in the conventional treatment group compared with 3.1/100 patient-years in the

intensive group for a risk reduction of 69% (NNT = 15). There also was evidence of stabilization of baseline neuropathy with intensive treatment. In addition, the benefit of intensive control may persist even after such a regimen is loosened: In a 4-year follow-up of the

DCCT, patients who had been in the intensive treatment group showed an ongoing risk reduction for retinopathy and nephropathy despite increasing hyperglycemia.⁸ Data on neuropathy was not included. The limitations of the intensive treatment approach are cost, pa-

tient compliance, and the risk of symptomatic hypoglycemia.

Intensive treatment with sulphonylureas in non-insulin dependent diabetes mellitus may also be effective in reducing the incidence and progression of neuropathy.²¹ The United Kingdom Prospective Diabetic Study (UKPDS) was a prospective randomized multicenter trial on the risk of complications from type 2 diabetes in 3,867 newly diagnosed patients, age 48 to 60, treated intensively with sulphonylureas or insulin compared with conventional treatment. Patients in the intensive treatment group had a 25% risk reduction in microvascular endpoints ($p=0.0099$) compared with conventional treatment. Most of this was due to fewer cases of retinal photocoagulation. There was no statistically significant differences at 10 years in the 2 groups for vibration perception thresholds in the big toe, in the proportion of patients with absent ankle or knee DTR, in heart-rate responses to deep breathing and standing, or in the proportion of patients with impotence. At 15 years, the risk reduction for increased vibration perception thresholds in the big toe was 0.60 in the intensively treated group compared with the conventional group ($p=0.0052$). Whereas pancreatic transplantation halts the progression of neuropathy, these diabetes patients are end-stage with severe neuropathy and no improvement in the neuropathy occurs, even after 10 years of follow-up.^{22,23}

Symptomatic therapies are important, particularly with painful diabetic polyneuropathy. Simple measures, such as a bed cradle, for allodynia may be useful. (A bed cradle is a frame that attaches to the foot of the bed and keeps the sheets from rubbing on the feet.) A recent randomized controlled trial of therapeutic footwear on foot reulceration in diabetic patients without significant foot deformities compared the cumulative percentage of participants with recurrent foot ulceration over a two-year period.²⁴ The patients were randomized to therapeutic shoes with cork inserts, therapeutic shoes with pre-

fabricated inserts, or a control group that wore normal footwear. There were no statistically significant differences in ulcers or ulcer episodes between groups. Patients with neuropathic pain or with a mutilating arthropathy may still benefit from modified footwear.^{2,25}

Intensively treated patients [HbA_{1c} 6.5 to 7.5] had a 25% risk reduction in microvascular endpoints

Medical treatment of painful neuropathy includes antidepressants, anticonvulsants, analgesics, opiates, antiarrhythmics, and topical agents (Table 2). A systematic approach with neuropathic pain agents, beginning at low doses and gradually increasing until adequate pain relief or unwanted side effects occur is recommended. The most appropriate pharmacologic agent will vary from patient to patient. Limited direct comparison of these medications has been studied.^{11,26}

A small, randomized crossover trial comparing gabapentin with amitriptyline showed no significant difference in analgesic efficacy. The side effects were similar with the exception of weight gain with amitriptyline. No comparison data for the older population is available. Gabapentin is a good first choice of medication in the older population due to its limited side-effect profile and lack of drug-drug interactions.²⁷ This is offset in part, however, by the expense of the drug.

NSAIDs are helpful on an as-needed basis, but the risk of gastric ulcer with chronic use remains a concern.


The tricyclic antidepressants are probably the most effective of the neuropathic pain therapies, but must be used judiciously in older patients due

to their anticholinergic side effects, including somnolence, confusion, postural hypotension, and urinary retention in men.¹¹ A low dose at night (10 mg), particularly in patients with insomnia from neuropathic pain, can greatly improve quality of life while limiting the cognitive side effects.

Anticonvulsant medications, such as carbamazepine, can be useful, particularly if lancinating pains are prominent. If adequate pain relief has been obtained for 3 months or more, a gradual taper of pain medication may be attempted.

For refractory pain, a referral to a pain clinic may be appropriate.

Conclusion

Diabetic polyneuropathy is a common complication of diabetes mellitus with significant morbidity and impairment of quality of life. The diagnosis is based upon an appropriate clinical history with a neurologic examination that demonstrates a distal symmetrical sensory > motor neuropathy. Supportive studies include EMG/nerve conduction studies and laboratory studies to exclude treatable causes of neuropathy. Early diagnosis is important to prevent complications such as chronic ulcers and amputation. Intensive glucose control is the only therapy proven to reduce the incidence or slow the progression of diabetic polyneuropathy. Symptomatic treatment for neuropathic pain can greatly improve the quality of life of patients with diabetic polyneuropathy. 

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