

THE SPECTRUM OF DIABETIC NEUROPATHY

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PREVALENCE

Diabetes Mellitus (DM) is the most common cause of neuropathy in the Western world. There are 12×10^6 patients with non-insulin dependent DM (NIDDM) in the USA and 1×10^6 patients with insulin dependent DM (IDDM). At present 20% of people >age 65 have DM, by 2010 it will be >30%. Neuropathy occurs in NIDDM and IDDM, but may develop sooner after diagnosis in NIDDM. While a cross-sectional study of 6487 patients found a 28.5% prevalence of neuropathy (Young et al 1993), other series reported a range of 5-100% (Thomas and Tomlinson 1993), likely due to differences in study populations, the definition of diabetic neuropathy, and the method of ascertainment, i.e. symptoms only, signs and symptoms, electromyography/nerve conduction studies (EMG/NCS), or composite parameters. Using a comprehensive evaluation methods, neuropathy was present in 66% of diabetic patients in one series (Dyck et al 1993). 8% have neuropathy at the time of diagnosis of DM, 50% after 25 years. The commonest neuropathy was polyneuropathy, with a prevalence of 54% in IDDM, and 45% in NIDDM, while focal forms account for 25%. The neuropathy was often asymptomatic. \approx 2% of diabetic children have neuropathy (Thomas and Tomlinson 1993). The prevalence increases with the duration of DM (Table 1).

RISK FACTORS

Age, dyslipidemia, hypertension, peripheral vascular disease, weight changes and other end-organ complications raise the likelihood of neuropathy. Gender may be a differential factor, depending on the type of neuropathy. Glycemic control is most important: A 60% risk reduction is associated with a HgA1c of 7 vs. 9%, with further reduction below 7%. Only speculation is possible at present about the role of genetic factors.

CLASSIFICATION OF DIABETIC NEUROPATHY

Diabetic neuropathy is heterogeneous (Thomas and Tomlinson 1993). Table 2 shows one classification. Importantly many patients present with >1 form of neuropathy, e.g. polyneuropathy and carpal tunnel syndrome (CTS).

DISTAL SENSORY AND SENSORIMOTOR POLYNEUROPATHY

Symptoms and Signs

A distal sensory neuropathy with an insidious onset is the most common neuropathy in patients with diabetes (Thomas and Tomlinson 1993). Initially small and large fibers may be affected in varying degrees, but later typically both are. This is a length-dependent process, with the most distal portions of the longest nerves affected earliest. Thus, the earliest symptoms typically

involve the toes, and then ascend. The arms are involved later, less often and less severely, also in a distal-to-proximal pattern. Early arm involvement warrants consideration of entrapment neuropathies. If severe, the midline abdomen and the head may be involved. The most common symptoms are numbness, tingling, and pain. Commonly patients present just because of foot pain. It is important to recognize that patients will use different terms to describe the abnormal sensation: Deep, aching, stabbing tingling, burning, “like water running over skin, discomfort heightened if bed sheet touch feet or by walking around barefoot (both suggesting allodynia), electric shock. Patients may see podiatrists for what they consider a local foot problem. The pain is often worst at night, disturbing sleep, and the patient may have to sleep with the feet uncovered. Despite the pain, there is numbness, but patients may not volunteer or recognize this. Or they may describe the feeling as “dead skin”, “wearing gloves or socks”. Restless leg syndrome (RLS) and periodic leg movement of sleep (PLMS) are common, but complaints are often not volunteered. Gait ataxia may be reported. Patients should be asked to quantitate the number of falls. Distal weakness is typically minor and occurs later. Some patients experience cramps. Examination generally demonstrates distal panmodal sensory loss, with reduced or absent ankle jerks. Testing pin prick and vibration sense in a stereotypical distal to proximal pattern in the authors’ experience significantly raises the test sensibility.

Diagnosis

~20% of neuropathy patients remain without a etiologic diagnosis after routine lab studies including B12, folate, ANA, rheumatoid factor, ESR, immunofixation electrophoresis, RPR, TSH, CBC, and comprehensive metabolic panel. Recent reports suggest that some of these have impaired glucose tolerance (IGT) with glucose of 144-199 mg/dl in a 2 hr glucose tolerance test (Novella et al 2001, Russell and Feldman 2001, Singleton et al 2001). The more convenient test of HgA1c is insensitive. ≥30% of diabetics have other reasons for neuropathy; these causes must be sought. HIV and HCV antibody testing is often strongly indicated, considering that HIV has spread to non-classical risk groups and that HCV has a prevalence of 0.5-2% worldwide with 4x10⁶ people infected in the USA. When RLS or PLMS are suspected, complete iron studies should be obtained. It is not trivial that a diagnosis of DM does not decrease the likelihood of unrelated neuromuscular problems, e.g. CMT or ALS.

Electrodiagnostic Studies (EMG/NCS)

This neuropathy is usually classified as both axonal and demyelinating (Donofrio and Albers 1990). Exclusively or predominantly demyelinating changes warrant consideration of chronic inflammatory demyelinating neuropathies. The lower limbs are affected first and most severely. The earliest and most sensitive findings are abnormal sensory NCS, which demonstrate conduction slowing and decreased amplitude. In more severe cases sensory responses disappear. Motor NCS may demonstrate slowing even in the absence of neuropathic symptoms or signs, worse in symptomatic patients. Motor amplitudes decrease in advanced cases. EMG may be normal in mild or asymptomatic subjects, but demonstrates denervation in more severe cases, worse distally (Thomas and Tomlinson 1993, Dumitru 1995).

Sural Nerve Biopsy

Findings include loss of myelinated and unmyelinated axons. Demyelination is also seen by fiber teasing. The walls of small neural blood vessels, particularly endoneurial capillaries, are thickened due to reduplication of the basal lamina (Thomas and Tomlinson 1993).

Pathogenesis

Metabolic and vascular/hypoxic factors appear to be involved in diabetic polyneuropathy (Vinik 1999b). Advanced glycosylation end products may damage capillaries, inhibit axonal transport,

Na⁺/K⁺-ATPase activity and cause axonal degeneration. Hyperglycemia and increased intracellular glucose may saturate normal glycolysis. Extra glucose may enter the polyol pathway and activates aldose, which converts it to fructose and sorbitol. Their accumulation results in reduced nerve myoinositol and membrane Na⁺/K⁺-ATPase activity, impaired axonal transport, and structural damage. Nerve ischemia may result from increased endoneurial vascular resistance to hyperglycemic blood. In experimental animals, the metabolism of nerve growth factor (NGF) is impaired, which is the basis for clinical studies.

Treatment and primary and secondary Prevention

Control of hyperglycemia delays the appearance of neuropathy and slows progression. The Diabetes Control and Complications Trial found that intensive IDDM therapy reduced the frequency of neuropathy by 60% over 5 years (DCCT Research Group 1993). Pancreatic transplantation appears to halt the progression of diabetic neuropathy, but does not clearly reverse existing neuropathy (Kennedy et al 1990, Navarro et al 1997).

Aldose reductase inhibitors (ARIs) such as sorbinil, alrestatin and tolrestat have been studied as a means to prevent or improve polyneuropathy. They act by reducing the flux of glucose through the polyol pathway. The many human clinical trials of ARIs had mixed results, and no clear conclusion can be drawn regarding their benefits (Pfeifer et al 1997; Nicolucci et al 1996). A recent trial showed that doses producing >80% suppression of nerve sorbitol content were required to demonstrate efficacy, so that even residual aldose reductase levels might be neurotoxic (Green et al 1999).

A randomized, double-blind, placebo-controlled phase II study of NGF found improved sensation subjectively and objectively compared to placebo (Apfel et al 1998).

Foot Care

25% of DM patients develop foot complications at some point (Most and Sinnock 1983), and they account for ~50% of nontraumatic lower limb amputations in the USA (Bild et al 1989). Plantar ulceration often precedes amputation (Pecoraro et al 1991). Patients develop foot problems for several reasons (Boulton 1990, Stevens et al 1992, Cavanagh et al 1996, Mayfield et al 1998): Loss of protective sensation may result in painless injuries. Intrinsic foot muscle atrophy can lead to foot deformities and an abnormal distribution of weight with walking, producing increased plantar pressures. Autonomic neuropathy (to be discussed below) causes dry skin which can crack, and arteriovenous shunting with altered skin and bone perfusion. These factors may lead to foot deformities (a Charcot foot) with disruption of the normal bony architecture and with plantar ulcers. While there are no randomized, controlled trials, careful daily inspection, trimming of nails, and proper footwear appear beneficial (Mayfield et al 1998).

Pain Management

This is the subject of a separate talk.

SMALL FIBER POLYNEUROPATHY

Small fibers may be the first to be affected, as in early neuropathy sensory and sexual symptoms are 6x and 4x as common as motor symptoms (Thomas 1997). Some patients continue to have a selective small-fiber polyneuropathy (Brown et al 1976, Said et al 1983, Kennedy and Wendelschafer-Crabb 1996, Kennedy et al 1996, Holland et al 1998, Hermann et al 1999). Pain is the main complaint, most commonly distally, described in similar terms as discussed above. Autonomic dysfunction is frequently present. On exam there is distal sensory loss affecting pain and temperature, with relative preservation of the large fiber functions vibration, proprioception, reflexes and strength. NCS are normal or minimally abnormal, since such tests assess primarily

large, fast-conducting fibers. Quantitative sensory testing (QST) is abnormal in 60% 100%. Autonomic testing may be abnormal. Biopsies show predominantly small fiber loss, but may be normal. Skin biopsies demonstrate abnormalities of intra-epidermal nerves. Treatment focuses on glucose and pain control.

AUTONOMIC NEUROPATHY

Visceral autonomic neuropathy was present in 7% of IDDM patients and 5% of NIDDM patients in one series (Dyck et al 1993), but subclinical evidence is present in 30% after 10 years. The variable clinical features can be mild or incapacitating (Thomas and Tomlinson 1993) (Table 3). Only the major manifestations are discussed here.

Treatment of Orthostatic Hypotension

Non-pharmacological measures include:

- Avoid sudden changes in body posture to the head-up position, particularly in warm weather, and after taking a warm bath, both of which produce cutaneous vasodilation.
- Avoid drugs that worsen hypotension, e.g. tricyclic antidepressants and phenothiazines.
- Small, frequent meals to lessen hypotension after large carbohydrate-containing meals.
- Reduce activities involving straining, since increased intra-abdominal and intra-thoracic pressure decreases venous return.
- Elevation of the head of the bed 18 inches at night improved symptoms in a small series of patients with orthostatic hypotension of various causes (MacLean and Allen 1940).
- Compressive garments over the legs and abdomen (Schatz et al 1963, Levin et al 1964, Lewis and Dunn 1967, Sheps 1976).
- An inflatable abdominal band (Tanaka et al 1997).
- A low portable chair used prn when patients feel faint (Smit et al 1997).

Use of many drugs is based on accepted practice rather than controlled studies. Plasma expansion through salt intake or prostaglandin inhibitors such as ibuprofen or indomethacin is recommended (Onrot et al 1986). One of the first effective treatments was plasma expansion with 9-alpha-fluorohydrocortisone (Hickler et al 1959, Bannister et al 1969). A study of 14 patients showed symptomatic and objective improvement (Campbell et al 1976). The effects are not immediate, but occur over 1-2 weeks. Supine hypertension, hypokalemia, and hypomagnesemia may occur. Fluid overload must be avoided, particularly in congestive heart failure (Chobanian et al 1979, Robertson and Davis 1995). A starting dose is 50 g qhs, with slow titration to a maximum of 200 g. The dose can ultimately be titrated up to 400 g, with greater risk of hypokalemia, fluid retention, hypertension and congestive heart failure.

Sympathomimetic drugs can be helpful. Ephedrine 15-45 mg tid is given upon awakening, at lunch and dinner. Side effects are tremulousness, irritability, insomnia, hypertension, tachycardia, poor appetite and urinary retention (Mathias 1998). An alternative is midodrine, an alpha agonist which activates alpha-1 receptors on arterioles and veins to increase total peripheral resistance (Zachariah et al 1986, McTavish and Goa 1989). The usual dose is 2.5-10 mg tid. As it does not cross the blood-brain barrier, it has fewer central side effects. Several double-blind, placebo-controlled studies have documented its efficacy (Low et al 1997, Kaufman et al 1988, Wright et al 1998). Adverse effects include piloerection, pruritus, paresthesiae, urinary retention, and supine hypertension. These drugs must be used cautiously with ischemic heart disease, arrhythmias and peripheral vascular disease.

Dihydroergotamine combined with caffeine, indomethacin, and the alpha-2 adrenergic antagonist yohimbine is used in refractory patients (Vinik 1999a,b). In an animal model of orthostatic

hypotension, yohimbine delayed the fall in BP elicited by head-up tilting, but did not modify its magnitude (Verwaerde et al 1997).

Beta blockers have shown efficacy in some open-label studies of patients with orthostatic hypotension due to varying etiologies (Chobanian et al 1977, Brevetti et al 1981, Man in't Veld and Schalekamp 1981), but a double-blind, placebo-controlled crossover study of 8 patients with diabetic autonomic neuropathy and orthostatic hypotension showed no benefit (Dejgaard and Hilsted 1988).

Treatment of Gastroparesis

Multiple small feedings and reduced dietary fat and fiber have been advocated (Hilsted and Low 1997, Verne and Sninsky 1998, Vinik 1999a,b). Most drugs are prokinetic, e.g. metoclopramide, cisapride, or domperidone.

Metoclopramide stimulates acetylcholine release in the myenteric plexus and is a dopamine antagonist and antiemetic (Verne and Sninsky 1998). There have been 1 open, 2 single-blind and 5 double-blind trials. The single-blind and double-blind trials demonstrated improvement in gastric emptying, while the open trials showed no improvement (Sturm et al 1999). Extrapyramidal symptoms, e.g. dystonic reactions, parkinsonism, akathisia, and tardive dyskinesia, and endocrine disturbances, i.e. galactorrhea, amenorrhea, gynecomastia, and hyperprolactinemia occur. The usual dose is 10 mg 30 minutes before meals and qhs.

Cisapride increases gut motility by increasing acetylcholine release from postganglionic myenteric neurons (Verne and Sninsky 1998). Improved gastric emptying was shown in 10 open and 7 double-blind trials (Sturm et al 1999). It appears to maintain efficacy in long-term use (Kendall et al 1997). Lacking the dopaminergic activity of metoclopramide, it avoids extrapyramidal and other side effects. It may be contraindicated with heart disease or abnormal EKGs. Usually 10-20 mg is given 15-30 min before meals and qhs.

Erythromycin is effective in accelerating gastric emptying, possibly by stimulating gut motilin receptors (Peeters et al 1989). It may be used po or iv (Richards et al 1993, DiBaise and Quigley 1999). There have been 5 open trials with 71 patients, with a mean improvement in gastric emptying of >40% (Sturm et al 1999). A single-blind trial also demonstrated an improvement in gastric emptying of 50% (Sturm et al 1999).

Domperidone has demonstrated efficacy, but fewer patients were studied: 2 open trials of 18 patients and 2 double-blind trials of 28 patients showed improved gastric emptying (Sturm et al 1999). A double-blind, randomized trial found that domperidone and metoclopramide are equally effective (Patterson et al 1999).

An analysis of 36 studies of prokinetic agents found that the 4 agents improve gastric emptying times and symptoms (Sturm et al 1999). Improvement in gastric emptying time was greatest with erythromycin, followed by domperidone, cisapride and metoclopramide. Symptoms improved most with erythromycin, then domperidone, then metoclopramide, then cisapride. The ultimate choice is usually influenced by cost, availability, and side effects.

Persistent vomiting may require surgery: Feeding jejunostomy to bypass an atonic stomach has been advocated (Verne and Sninsky 1998). Radical surgery with resection of a large portion of the stomach and performance of a Roux-en-Y loop, has been successful in a small series

(Ejskjaer et al 1999). In one series of 9 patients with gastroparesis, 5 of whom had diabetes, gastric pacing accelerated gastric emptying and improved symptoms (McCallum et al 1998).

Treatment of Diarrhea

This often results from bacterial overgrowth, diagnosed by hydrogen breath test. Broad-spectrum antibiotics are commonly used to treat diarrhea, either when the breath test is positive or empirically. Several regimens have been advocated: Ampicillin or tetracycline 250 mg q8h or metronidazole 500 mg q6 or 750 mg q8h X 3 wks (Vinik 1999a,b). Amoxicillin 875mg and clavulanate potassium bid X 14 days (Verne and Sninsky 1998). Long-term use of metronidazole can cause neuropathy.

Cholestyramine can be used to chelate bile salts if the hydrogen breath test is normal, or if patients fail antibiotics (Vinik 1999a,b). Diphenoxylate with atropine or loperamide are options. Octreotide (a somatostatin analog) 50-75 g sq bid was effective in a single patient (Tsai et al 1986). A recent study showed that octreotide accelerated gastric emptying, inhibited small bowel transit, reduced ileocolonic bolus transfers, inhibited post-prandial colonic tonic response, and increased colonic phasic pressure activity in healthy volunteers; it thus may be useful for diarrhea (Von der Ohe et al 1995).

Treatment of the Neurogenic Bladder

Lower urinary tract dysfunction occurs in 26% to 87% of diabetics (Frimodt-Moller 1980). Patients have a decreased ability to sense a distended bladder, due to loss of autonomic afferents. Therefore they urinate less often and develop a hypocontractile bladder, urinary retention, frequent UTIs, poor stream, dribbling, and overflow incontinence (Buck et al 1976, Frimodt-Moller 1980, Menendez et al 1996), Hilsted and Low 1997, Vinik 1999a,b). Patients need a referral to a urologist for cystometrography. If abnormal, scheduled voiding is recommended, often coupled with manual bladder squeezing to start urination (Crede's maneuver). Bethanechol 10-30 mg tid, a parasympathomimetic, may be helpful. Some require indwelling or intermittent catheterization. Bladder neck or size reduction surgery has been advocated (Watanabe and Miyagawa 1999).

Treatment of Sexual Dysfunction

Erectile dysfunction (ED) affects 35-75% of diabetic men (Rundles 1945, Rubin and Babbott 1958, McCulloch et al 1980, Zemel 1988). Efficacy of sildenafil was shown in a randomized, double-blind, placebo-controlled study (Rendell et al 1999). By inhibiting the enzyme phosphodiesterase type 5, it increases nitric oxide and facilitates smooth muscle relaxation and inflow of blood. Side effects include headache, dyspepsia, and respiratory tract disorder. The dose is 25-100 mg 1 hr before intercourse. Other similar drugs may come on the market soon. Other options include vacuum devices, rigid and inflatable penile implants (Saulie and Campbell 1997, Spollett 1999). Corpus cavernosum injection with papaverine or alprostadil is successful in ~90% (Virag et al 1984, Spollett 1999). Yohimbine, an alpha-2 adrenergic antagonist, is occasionally used. A meta-analysis of 7 randomized clinical trials found it to be more effective than placebo (Ernst and Pitter 1998).

CRANIAL NEUROPATHIES

Patients are mostly above age 50. The onset is typically abrupt, and may be painless or associated with a headache. The oculomotor nerve (CN III) is most often affected, usually but not always sparing the pupil. Dysfunction of the trochlear (CN IV) and abducens nerves (CN VI) is less common. Sometimes >1 nerve is involved. There is no specific treatment. Gradual recovery is typical. While the facial (CN VII) and other cranial neuropathies are associated with DM, causality is uncertain (Asbury 1987, Thomas and Tomlinson 1993). Bell palsy should be

treated in standard fashion in diabetics, though blood sugars must be followed closely if steroids are given.

LIMB MONONEUROPATHIES

Compression and entrapment neuropathies are common without and with diabetes, and causality of DM is uncertain. With a prevalence of 11% in IDDM and 6% in NIDDM CTS, due to median nerve involvement at the wrist, is most common. Asymptomatic CTS is even more frequent (Dyck 1993). Ulnar neuropathy at the elbow is common too. Symptoms of pain, numbness and weakness develop slowly. Treatment, conservative or surgical, is empiric. A co-existing polyneuropathy does not preclude surgery, but which neuropathy is responsible for the symptoms must be carefully considered (al-Quattan et al 1994).

Nerve palsies may also be abrupt and painful, possibly due to ischemia. Common examples include the radial nerve (wrist drop), peroneal nerve (foot drop), femoral nerve (quadriceps weakness), and lateral femoral cutaneous nerve (meralgia paresthetica). EMG/NCS reveal axon loss. Depending on severity and proximal vs. distal lesion sites recovery takes months to years. Distal strength often recovers incompletely. If multiple nerve are affected, a mononeuropathy multiplex results. There is no specific treatment, but with multi-nerve involvement immunomodulation has been proposed (see below).

DIABETIC THORACOABDOMINAL/TRUNCAL NEUROPATHY/RADICULOPATHY

This is characterized by pain around the abdomen or lower chest described as burning, stabbing, boring, belt-like or deep aching. Cutaneous hyperesthesia and abdominal wall weakness occur. While onset is unilateral, symptoms may spread to the opposite side as well as to higher or lower dermatomes. Often patients are referred to neurologists only after cardiac and gastrointestinal disorders have been investigated. They typically are over age 50, have NIDDM with polyneuropathy and a history of recent weight loss. NCS/EMG may be diagnostic of a focal neuropathy and show paraspinal denervation (Thomas and Tomlinson 1993). Once structural abnormalities are ruled out by imaging studies, treatment consists of pain management. Gradual improvement is typical.

ASYMMETRIC LOWER LIMB MOTOR NEUROPATHY (DIABETIC AMYOTROPHY)

Synonyms include proximal diabetic neuropathy, diabetic polyradiculopathy, diabetic femoral neuropathy, diabetic lumbar plexopathy, and diabetic lumbosacral plexus neuropathy. The prevalence is ~0.1%, patients are usually men above age 50 with poorly controlled NIDDM and often recent weight loss. Pain is almost always at the onset, usually in the territory of lower thoracic and upper lumbar roots. This may be preceded by anorexia. Paresthesiae and hyperesthesiae are common. Weakness, generally in the upper legs, follows the pain. On exam, weakness is most frequently in a L2-4 distribution, affecting the iliopsoas, quadriceps, and adductor, and sparing hip extensors and hamstrings. It may be unilateral or bilateral and asymmetric. Distal sensorimotor or sensory polyneuropathy usually coexists. Knee and ankle jerks are lost in most (Bastron and Thomas 1981). The condition may progress over 1-2 weeks or year. Pain typically is worst at onset, and gradually subsides. Often strength improves over 18 months, but incompletely.

EMG reveals fibrillations and positive sharp waves in leg, thoracic or lumbar paraspinal muscles, most commonly L2-4; low thoracic and L5-S1 levels may be affected.

The cause is a multifocal, perivascular, polymorphonuclear/mononuclear vasculitis with endoneural or subperineural IgM and endothelial activated complement (C5b-9) deposits, that produces

ischemia and myelinated/unmyelinated fiber loss and involves lumbosacral roots plexus, and peripheral nerves (Llewelyn et al 1998, Dyck et al 1999).

Traditionally no treatment was given other than DM control. However, the inflammatory changes on biopsy have lead to trials of immunomodulating agents. Prednisone, IVIG and plasmapheresis showed promise in open-label, uncontrolled studies: Disease progression was halted in some, others improved. However, since untreated patients also improve, the efficacy of these treatments remains unproven (Krendel et al 1995, Krendel et al 1997, Pascoe et al 1997, Jaradeh et al 1999).

OUTLOOK

Diabetic neuropathies present several challenges. Somewhat surprisingly these include the definition and diagnosis of DM. Recent studies suggest that DM or at least pre-DM, defined as glucose intolerance, which is a risk factor for end organ damage, may be underdiagnosed, possibly vastly so. Paradoxically, another challenge arises from the fact that essentially “everybody has it”, but not every diabetic has the same type or just one type of neuropathy. Patients and caregivers alike may be overwhelmed by the diversity of co-existing symptoms, which carries the risk of overlooking some, such as ED, RLS or PMLS (or OSA). Stopping the diagnostic work-up, once one etiology has been found, risks overlooking several others, that might be treatable. It is unfortunate if a diagnosis of small fiber neuropathy is overlooked in patients with intense neuropathic pain, who have no neurologic findings and normal EMG/NCS. QST often provides objective evidence of neurologic impairment. The risk of falls, (hip) fractures and other injuries with a risk of long term morbidity and death, must be addressed in patients with large fiber neuropathy, poor proprioception and ataxia, as well as those with orthostatic hypotension and autonomic neuropathy, both isolated and as part of the generalized neuropathy. This involves prevention and treatment of osteoporosis, patient and caregiver education, emphasis on gait training and use of ambulatory aids and “home security”. Intensive foot ulcer prevention and treatment is mandatory. Chronic pain and disability almost invariably leads to depression, which must be sought and treated. Insomnia arising from pain o RLS/PLMS must be dealt with. Importantly therapeutic options are limited by side effects, as many pain drugs can worsen orthostatic hypotension, ED and OSA, as well as cognitive impairment, often mild and subclinical in the elderly.

Table 1.
Prevalence of Diabetic Neuropathy relative to Duration of DM

Reference	Initial Prevalence	Time of initial Prevalence	Later Prevalence	Time of later Prevalence
Pirart 1978	7.5%	At diagnosis	50%	25 yrs later
Palumbo et al 1978	4%	Within 5 yrs	15%	20 yrs later
Young et al 1993	20.8%	<5 yrs later	36.8%	>10 yrs later
Partanen et al 1995	8.3%	At diagnosis	41.9%	10 yrs later

Table 2.
Classification of Diabetic Neuropathies

- Symmetric polyneuropathies
 - Chronic sensory or sensorimotor
 - Acute or chronic selective small-fiber painful
 - Autonomic
 - Symmetric, lower limb, motor

- Focal and multifocal neuropathies
 - Cranial nerves
 - Asymm. trunk/limb, single/multiple nerves
 - CIDP

- Mixed forms

Table 3.

Clinical Features of Diabetic Autonomic Neuropathy

- Cardiovascular disturbances
 - Abnormalities of heart rate
 - Orthostatic hypotension
 - Edema
 - Hypothermia
- Pulmonary
 - Respiratory arrest (rare)
 - (carotid body denervation?)
- Gastrointestinal disturbances
 - Esophageal, gastric, gallbladder, duodenal, colonic atony
 - Vomiting
 - Early satiety
 - Loss of appetite
 - Diarrhea (postprandial, nocturnal)
 - Anal sphincter weakness, incontinence
 - ? PUD due to vagal denervation
- Genitourinary disturbances
 - Frequency, straining, stream, dribbling
 - Overflow incontinence
 - Infection
 - Retrograde ejaculation
 - Impaired genital sensation
 - Erectile dysfunction
 - Ejaculatory dysfunction
 - Orgasmic dysfunction
 - Decreased lubrication sexual dysfunction
- Unawareness of hypoglycemia
- Skin
 - Abnormalities of sweating
 - Abnl sweating (gustatory, cheese, acid, EtOH)
 - Impaired inflammatory response to trauma
- Cranial Nerves
 - Pupillary dysfunction
 - lacrimation

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