Malaysian Journal of Medical Sciences, Vol. 10, No. 2, July 2003 (27-30)

REVIEW ARTICLE

MANAGEMENT OF DIABETIC NEUROPATHY

Raymond Azman Ali

Senior Consultant Neurologist
Department of Medicine, Medical Faculty UKM

Diabetes mellitus is the commonest cause of neuropathy worldwide. Diabetic neuropathy (DN) develops in about 4-10% of diabetic patients after 5 years and in 15% after 20 years.Four main mechanisms have been postulated to underlie the pathogenesis of DN. Diabetic neuropathy can be divided into symmetrical and asymmetrical neuropathies. Diabetic Autonomic Neuropathy (DAN) parallels the severity of DSN, and affects primarily the cardiovascular, gastrointestinal, genitourinary and integumentary systems. The cornerstone of treatment of diabetic neuropathy is optimization of glycaemic control. Future treatments for diabetic neuropathy should address the underlying pathogenesis.

Key words *: Diabetes Mellitus, Neuropathy, Management*

Diabetes mellitus is the commonest cause of neuropathy worldwide. Diabetic neuropathy (DN) develops in about 4-10% of diabetic patients after 5 years and in 15% after 20 years. (1) Longer duration of diabetes, type I diabetes mellitus, the male gender and co-existent hypertension are risk factors for the development of DN. (2) The diagnosis of diabetic neuropathy must be based on clinical symptoms, objective neurological signs, and electrodiagnostic confirmation. (3)

Four main mechanisms have been postulated to underlie the pathogenesis of DN: (1) metabolic processes directly affecting nerve fibres, (2) endoneurial microvascular disease, (3) autoimmune inflammation, and (4) deranged neurotrophic support. (2) The metabolic hypothesis states that prolonged hyperglycaemia leads activation of the polyol pathway through the enzyme aldose reductase and accumulation of sorbitol and fructose in affected nerves, non-enzymatic glycosylation of structural nerve proteins and depletion of nerve myoinositol. These changes lead to abnormal neuronal and axonal metabolism, which in turn, leads to impaired axonal transport. However, this theory is not fully supported by pathological studies and clinical trials with aldose reductase inhibitors. Hyperglycaemia also leads to increased endoneurial vascular resistance and reduces nerve blood flow.

Microvascular abnormalities lead to endoneurial hypoxia and subsequent inhibition of axonal transport and nerve infarction. Capillary damage leads to further decrease in blood flow and hypoxia and a vicious cycle is set in motion. Endoneurial hypoxia appears to be a more important pathogenetic mechanism in type 2 than in type 1 diabetes mellitus. The presence of inflammatory infiltrates in nerves of diabetic patients supports an autoimmune process. The role of neurotrophic factors is supported by the observation that NGF-associated small diameter sensory fibres are affected before involvement of the other fibre types. (4)

Diabetic neuropathy can be divided into symmetrical and asymmetrical neuropathies. Symmetrical diabetic neuropathies include distal symmetrical neuropathy (DSN), diabetic autonomic neuropathy (DAN), small fibre neuropathy (SFN) and large fibre neuropathy (LFN). Asymmetrical diabetic neuropathies include single or multiple cranial mononeuropathies (MCM), single or multiple somatic mononeuropathies (MSM), asymmetrical lumbosacral radiculoplexopathy (ALR), single or multiple monoradiculopathy (MM) and entrapment neuropathy (EN). In practice, patients often have multiple subtypes or overlap of these subtypes. Distal symmetrical neuropathy is the most common form of diabetic neuropathy. The predominant pathology is axonal degeneration affecting primarily the sensory nerves. Axonal

degeneration is due dying-back centripetal degeneration of peripheral axons. (5) In painful DSN, the principal fibres involved are the small myelinated and unmyelinated ones, whereas in painless DSN, large myelinated fibres are predominantly involved. Biopsies of the sural nerve show loss of myelinated fibres, acute axonal degeneration, some degree of demyelination and evidence of vasculopathy. Narrowing or closure of the endoneurial capillary lumen, thickening of the capillary wall, and marked redundancy of basement membranes characterize the latter. This type of neuropathy progresses slowly over months. Demyelination is less prominent and is probably the result of primary progressive axonal atrophy. The pathological process for MCM and MSM is thought to be small vessel occlusive disease. The precise location of the pathological lesion in ALR is unknown, but may be in the roots or plexus and due to occlusion of the vasa nervorum.

Patients with DSN initially complain of numbness and severe pain in the toes that ascend slowly over months. The hands become affected when the sensory symptoms reach knee level. Muscle weakness is less prominent, but difficulty in executing fine finger movements may be noted. Examination reveals wasting and weakness of the muscles of the hands and feet, diminished or absent tendon reflexes, glove-and-stocking anaesthesia, foot ulcers and rarely Charcot joints (particularly the small joints of the feet). Concomitant autonomic involvement parallels the severity of the neuropathy. Small fibre neuropathy (SFN) and large fibre neuropathy (LFN) are subtypes of DSN, with the former presenting with "burning feet" and the latter, a painless ataxic sensory neuropathy. SFN typically affects the Ad and C fibres.

DAN parallels the severity of DSN, and affects primarily the cardiovascular, gastrointestinal, genitourinary and integumentary systems. The spectrum of autonomic involvement varies from subclinical impairment of cardiovascular reflexes and sudomotor function, to severe cardiovascular, gastrointestinal, or genitourinary dysfunction. Orthostatic hypotension, resting tachycardia, a heart rate that does not vary with respiration, loss of sinus arrhythmia, silent myocardial infarction, symptoms of delayed gastric emptying, paroxysmal explosive nocturnal diarrhoea, constipation due to colonic atony, urinary retention with overflow incontinence, impotence, gustatory sweating, distal anhidrosis, constricted pupils and loss of awareness of hypoglycaemia are recognized features of DAN. Orthostatic hypotension is due to failure of the sympathetic nervous system to increase systemic vascular resistance in the erect posture, with impairment of compensatory cardiac acceleration. Resting tachycardia is due to vagal denervation of the heart. Early satiety, nausea, and postprandial bloating are the principal symptoms of delayed gastric emptying. Bacterial overgrowth in the gut may occur. Impotence, presenting as both erectile failure and retrograde ejaculation, occurs in about 30-60% of diabetic men; the majority of such patients also have some evidence of DSN. Distal anhidrosis causes compensatory facial and truncal sweating and heat intolerance.

MCM and MSM most commonly affect the 3rd, 4th, 6th and 7th cranial nerves, and median, ulnar and common peroneal nerves, respectively. Patients present with acute or subacute onset of a painful nerve palsy that recovers over weeks or months. The 3rd cranial nerve palsy in diabetics is painful and typically spares the pupils, reflecting injury to centrifascicular axons but sparing the peripherally situated papillary motor fibres of the oculomotor nerve. Rhinocerebral mucormycosis often occurs in poorly controlled diabetics, and presents with sudden fever, headache, and malaise, followed by periorbital pain, swelling, and induration. Nasal mucosal necrosis gives rise to the characteristic black turbinate. Vision loss, total ophthalmoplegia, and upper hemifacial sensory loss may occur. Left untreated, occlusion of the internal carotid artery, meningeal extension, obtundation and death may ensue. Treatment consists of surgical excision of affected tissues and intravenous amphotericin B. The mortality rate is close to 50% despite aggressive early treatment. MSM is due to nerve infarction and presents as acute focal pain, followed by weakness, atrophy and variable sensory loss.

Carpal and cubital tunnel syndromes are the most common presentations of diabetic EN. As the underlying pathology in EN is primarily focal segmental demyelination, the recovery is more rapid than MSM.

MM typically affects the T4-T12 roots in older patients with type 2 diabetes mellitus. Patients complain of truncal pain and dysaesthesias, described as burning, stabbing, boring, or beltlike pain. Contact with clothing or bedclothes can be unpleasant. Examination reveals hypaesthesia or hyperpathia over the thorax or abdomen. The symptoms may persist for several months before gradually subsiding. The differential diagnoses include intra-abdominal, intrathoracic, and

intraspinal diseases as well as herpes zoster.

ALR, also known as diabetic amyotrophy, most commonly affects middle-aged patients with type 2 diabetes mellitus. There is acute or subacute (over a few days) onset of asymmetric pain and weakness of the proximal lower limb muscles (iliopsoas, gluteus, thigh adductor, quadriceps, hamstring and anterior tibial muscles). The progression may be steady or stepwise and may continue for many months. Weight loss is present in over 50% of patients. Examination reveals profound atrophy and weakness of the proximal lower limb muscles and diminished or absent knee and ankle jerks. The nerve conduction study reveals prolongation of the femoral nerve latencies whilst needle electromyography shows neurogenic changes (prominent fibrillation potentials) in the affected muscles (thoracic and lumbar paraspinal muscles). ALR has a poor prognosis with recovery taking up to 24 months and persistent mild to moderate weakness is present in many patients. Pain usually recedes spontaneously long before motor strength begins to improve. Needle EMG reveals, neurogenic motor unit potential alterations in affected muscles, and prolongation of femoral If suspected, structural lumbar radiculoplexopathy or cauda equina lesions should be ruled out with an MRI. Older diabetics may present with a more symmetrical proximal lower limb paraparesis developing over weeks to months. Overlap with DSN is noted in up to 60% of patients.

The thoracic nerve roots (notably T4-T12) are the most commonly affected nerves in MM. Patients present with burning, stabbing, boring or beltlike chest or abdominal pain. Symptoms may take several months to subside.

An unusual syndrome in adult male type 2 diabetics is diabetic neuropathic cachexia. In this syndrome, there is massive weight loss (often > 40-50 kg) associated with painful symmetrical polyneuropathy or polyradiculoneuropathy, depression, insomnia, and impotence. (2)

It is important not to ascribe all unexplained pain, weakness, or sensory loss in diabetics to diabetic neuropathy. Appropriate investigations should be directed towards excluding treatable, often dangerous, differential diagnoses. Superimposed carpal tunnel syndrome, for instance, may mimic worsening diabetic neuropathy. Compressive lumbar radiculopathy or pelvic malignancy may masquerade as diabetic lumbosacral radiculoplexopathy. Painful third nerve palsy may actually be due to a ruptured berry aneurysm in the circle of Willis.

The cornerstone of treatment of diabetic neuropathy is optimization of glycaemic control. There is good evidence that good diabetic control is associated with less frequent and less severe peripheral nerve complications. The Diabetes Control and Complications Trial (1995) showed that intensive glucose management by insulin pump or by three or more daily insulin injections in patients with type 1 diabetes mellitus reduces the development of neuropathy by 64% at 5 years compared with conventional therapy. (6) The benefit from pancreatic transplantation is short-lived and clinical trials of myoinositol supplementation have shown conflicting results. Although aldose reductase inhibitors produce modest changes in nerve conduction and nerve pathology, clinical trials have failed to produce convincing clinical improvement. In uncontrolled studies, (7) high-dose intravenous immunoglobulin therapy has been reported to show benefit in patients with diabetic lumbosacral radiculoplexopathy.

Relief of pain is difficult, but certain drugs may be tried; these include amitriptyline, carbamazepine, gabapentin, mexiletine and topical capsaicin. One drug only should be tried at a time. An observation period of at least 3-4 weeks should be practiced before changing over to another medication. General measures, such as elevation of the head of the bed (by 15-25cm at night), increased salt (10-12 d/day) and water intake (>20 oz/day), eating more frequent small meals rather than a few large meals, and elastic body stockings may alleviate postural hypotension. Useful drugs include fludrocortisone (0.1-0.6 mg/day), midodrine, (8) phenylpropanolamine (25-50 mg t.d.s.) and ibuprofen (4oo mg q.i.d.). Gastrointestinal and genitourinary autonomic neuropathy must be treated symptomatically. Delayed gastric emptying can be treated with Metoclopramide and nocturnal diarrhoea with short courses of either tetracycline or erythromycin, or clonidine. Patients with a neurogenic bladder should be encouraged to adhere to a frequent voiding schedule during the day, which helps reduce the amount of residual urine. Manual abdominal compression or intermittent self-catheterization may be needed in more severe cases. Erectile dysfunction may respond to oral sildenafil, direct vasodilator injection into the copora cavernosa or penile implants. Both bladder involvement and erectile dysfunction must be treated in consultation with a urologist.

Daily inspection of the feet, regular pedicure, and prompt attention to seemingly trivial injuries

and infections are crucial aspects of proper skin care in diabetics with cutaneous sensory loss, impaired sweating, and vascular disease. These measures will minimize the risk of developing foot ulceration and distal joint destruction (acrodystrophic neuropathy).

Future treatments for diabetic neuropathy should address the underlying pathogenesis. Supporting evidence from more randomised clinical trials should be obtained before recommending the routine use of recombinant human nerve growth factor, antioxidants, NMDA antagonists and essential fatty acid supplementation. (9-12)

Correspondence:

Prof. Dr. Raymond Azman Ali MBBS (Hons) (Monash), M.Med (S'pore), M.Med (Mal.), MD (Monash), FRCP (Ireland), FAMM, FRCP (Glasg.)
Professor of Medicine
and Senior Consultant Neurologist,
Department of Medicine, Medical Faculty,
Universiti Kebangsaan Malaysia,
Jalan Yaacob Latif, Bandar Tun Razak,
56000 Cheras, Kuala Lumpur.

References

1. Martyn CN, Hughes RA. Epidemiology of peripheral neuropathy. *J Neurol Neurosurgery Psychiatry* 1997; **62**: 310-8.
2. Bosch EP, Smith BE. Disorders of the Peripheral Nerve. In: Bradley WG, Daroff RB, Fenichel GM, Marsden CD, eds. Neurology in Clinical Practice Third Edition. Oxford: Butterworth-Heinemann, 2000; 2045-130.
3. Thomas PK. Classification, differential diagnosis, and staging of diabetic neuropathy. *Diabetes* 1997; **46** Suppl 2: S54-S57.
4. Anand P. Neurotrophins and peripheral neuropathy. Phil Trans R Soc London 1996; **351**: 449-54.
5. Dyck PJ, Giannini C. Pathologic alterations in the diabetic neuropathies of humans: a review. *J Neuropathol Exp Neurol* 1997; **55**: 1181-93.
6. Diabetes Control and Complication Trial Research Group. The effect of intensive diabetes therapy on the development and progression of neuropathy. *Ann Intern Med* 1995; **122**: 561-8.
7. Krendel DA, Costigan DA, Hopkins LC. Successful treatment of neuropathies in patients with diabetes mellitus. *Arch Neurol* 1995; **52**: 1063-61.
8. Low PA, Gilden JL, Freeman R, et al. Efficacy of midodrine vs. placebo in neurogenic orthostatic hypotension. A randomised, double-blind multicenter study. Midodrine study group. *JAMA* 1997; **277**: 1046-51.
9. Apfel SC, Kessler JA, Adornato BT, et al. Recombinant human nerve growth factor in the treatment of diabetic polyneuropathy. *Neurology* 1998; **51**: 695-702.
10. Ziegler D, Gries FA. Alpha-lipoic acid in the treatment of diabetic peripheral and cardiac autonomic neuropathy. *Diabetes* 1997; **46** Suppl 2: S62-S66.
11. Nelson KA, Park KM, Roinovitz E, et al. High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. *Neurology* 1997: **48**: 1212-8.
12. Horrobin DF. Essential fatty acids in the management of impaired nerve function in diabetes. *Diabetes* 1997; **46** Suppl 2: S90-S93.