Treatment of diabetic neuropathy in the lower limb

Signs and symptoms of diabetic neuropathy may precede the onset of diabetes.

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Diabetic peripheral neuropathy (DPN) is defined as 'the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes: the diagnosis cannot be made without a clinical examination'. In fact, many of these symptoms and signs may precede the onset of diabetes.

Classification

The classification of diabetic neuropathy can be done in several ways: clinical presentation (symmetrical, focal or multifocal, or painful, paralytic and ataxic), type of fibres affected (motor, sensory, autonomic), or painful or non-painful.

The commonest presentation of peripheral neuropathy in diabetes is that of chronic sensorimotor neuropathy. This has an insidious onset, with most patients describing symptoms of burning pain, stabbing, shooting pain, hyperaesthesia or paraesthesiae. There is also commonly an exacerbation of symptoms at night. At the other end of the spectrum, patients may describe a feeling of total numbness in the feet and lower leg. Any patient who walks into the room in spite of extensive plantar ulceration has sensory neuropathy (Fig. 1).

Muscular pain secondary to injury to the motor neurons can present as night cramps, spasm or a dull ache. Motor signs and symptoms include imbalance when walking and ankle weakness

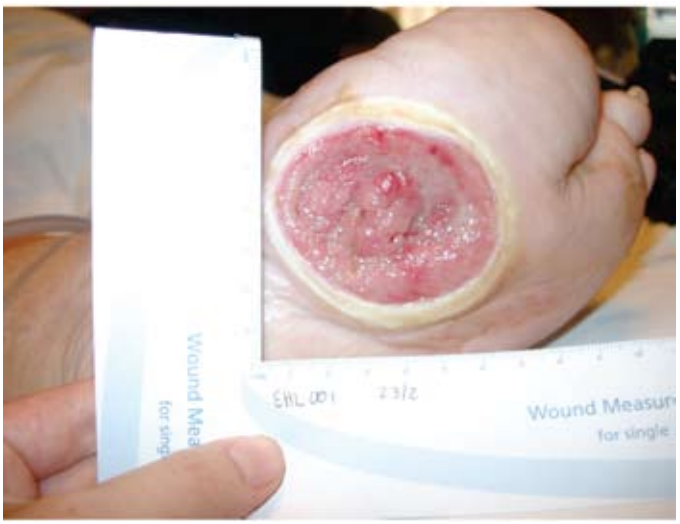

Fig. 1. A large ulcer with surrounding callus on a neuropathic diabetic foot showing previous toe amputation and deformity of the foot. This patient experienced no pain or discomfort when walking.

or even foot drop, usually asymmetrical at initial presentation. The classic signs of motor neuropathy are a high medial arch, claw toes and metatarsal head prominence with fatty pad thinning.

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Symptoms of autonomic neuropathy in the diabetic foot usually include dry, cracked skin, nail changes, transient mottling and discoloration of the skin and cold feet.

Confirmed clinical neuropathy, as diagnosed by a physician skilled in the proper examination technique, should also be backed up with the necessary quantitative sensory testing (e.g. electrophysiological tests, autonomic tests, etc). However, this does not mean that a basic neurological examination cannot be done by any health care worker in the field, trained in the proper manner to identify the diabetic foot at risk.

The two most prominent changes in a patient with mild diabetic distal neuropathy is a reduced or absent ankle reflex and distal gradient loss of large and small sensory fibre modalities, the so-called 'stocking-and-glove' sensory loss (Fig. 2).

Gradient loss to cold perception can be tested with a tip therm, which is used to assess whether the patient can distinguish between hot and cold tips on the skin surface. Examination with a 128 Hz tuning fork is the most practical way to check for the presence or absence of vibratory sensation in the feet, while the 10 g monofilament applied perpendicularly to the skin surface for 2 seconds in various sites is a straightforward way of detecting a lack of sensation.

Treatment

The non-modifiable risk factors for the development of DPN include age of the patient and the duration of diabetes. Young *et al.*, in the UK neuropathy study, showed that patients in the 20 - 29-year age group had an incidence of 5% DPN in contrast to 44% DPN in the 70 - 79-year group. Likewise in the Spanish neuropathy study, there was a 14% incidence among those diabetics who had had the disease for less than 5 years, while DPN reached nearly 50% in those who had been diagnosed more than 20 years previously.

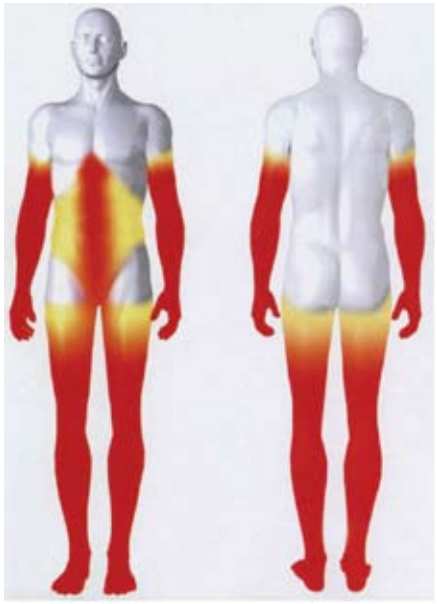

Fig. 2. The stocking and glove distribution of diabetic distal symmetrical polyneuropathy A distal dying back of the nerve fibres occurs, resulting in the involvement of the hands and feet in this pattern.

Modifiable risk factors in the disease process include hyperglycaemia, hypertension, hypercholesterolaemia, heavy alcohol abuse and smoking. In fact, hyperglycaemia has been shown to be the strongest risk factor for the development of DPN. In both the DCCT (Diabetes Control and Complications Trial) and the UKPDS (United Kingdom Prospective Diabetes Study), it was conclusively demonstrated that better glucose control prevents or slows the progression of diabetic neuropathy.

The management of DPN must take into account that neuropathic pain is commonly constant and associated with paroxysmal exacerbation of pain that does not follow a specific pattern. This can present a challenge in management for even the most skilled physician.

Although improved glycaemic control is proposed to control DPN, the expected pain reduction does not always correlate with an improved HbA_{1C} level. In fact, some patients often experience increased pain as better glucose control is achieved.

The treatment of DPN includes pharmacological and psychological approaches. Firstly, the clinician must make the patient aware that there is no magic pill or treatment available that will take away all the pain; a 40% reduction in pain is considered a good response to treatment.

Tricyclic antidepressants still serve as the mainstay for treatment of DPN. Amitriptyline in a therapeutic dosage range of 25 - 150 mg per day, with most or all the drug taken at night, remains a first-line agent in the treatment algorithm.

Many anticonvulsants have been shown to be effective in the management of DPN. Although the exact mechanism of benefit remains unknown for some of these drugs, they probably stabilise nerve fibre membranes and so suppress paroxysms of pain.

Carbamazapine is most effective in relieving the sharp, lancinating component of neuropathic pain rather than dull constant pain. Although it is well tolerated initially, 30 - 40% of patients will discontinue treatment within 1 year because of side-effects. Dosages of 200 mg three times per day are effective.

Gabapentin, related structurally to γ-aminobutyric acid, can be titrated up to a daily dose of 3 600 mg until a meaningful reduction in pain is reported. A starting dose of 300 mg at night can be increased every 3 - 5 days until a thrice-daily dosage is attained. Most adverse effects of the drug abate after 10 days of treatment. These are commonly drowsiness, fatigue and imbalance. Gabapentin has no interaction with other medications.

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Pregabalin possesses anticonvulsant, anxiolytic and analgesic properties. The advantage of this drug over gabapentin is the rapid improvement in pain in only 1 - 2 days. An effective dose is usually only attained if twice-daily medication is taken starting at 75 mg bd and increasing the dose up to 300 mg bd. It is important to note that pregabalin is cleared by the kidney, so reduced dosages are required in patients with creatinine clearances of less than 60 ml/min.

Duloxetine has proven efficacy as an antidepressant and reduces the pain intensity of DPN. It works better in combination with other classes of drugs such as tramadol hydrochloride.

Tramadol hydrochloride is an effective and unique pharmacological agent that reduces pain intensity in two ways. It acts as opioid agonist and as an activator of monoaminergic spinal inhibition of pain. Treatment should begin with 50 mg per day and be increased slowly to the maximum dose of 100 mg four times a day.

A 5% lidocaine patch applied to areas of maximal peripheral pain for weeks at a time until symptoms are under control, has been shown to be effective in DPN. Mood, walking ability, normal work and sleep all show considerable improvement.

Antioxidants

Alpha-lipoic acid given intravenously at a dose of 600 mg per day reduces neuropathic symptoms and deficits. Conversely, the results from oral use have not been convincing. In both the ALADIN II and ALADIN III studies no improvement was noted on oral treatment regimens. The initial improvement in symptoms noted in the first 3 weeks of ALADIN III occurred only during the intravenous dosage phase of the study.

Topical agents

Topical agents can also control symptoms in patients with DPN. Capsaicin, the active agent in chilli, depletes substance P, a neuropeptide necessary for the propagation of pain, when applied to the skin surface as a cream. The major adverse effect of capsaicin is its tendency to produce stinging, erythema and warmth at the application site. At best, capsaicin cream produces only mild to moderate pain relief.

Another mode of treatment involves the application of an adhesive clear plastic dressing on the dorsum of the foot from the medial to the lateral aspect. This can bring about an immediate amelioration in pain with muffling of the affected nerve endings.

Spinal cord stimulation

Spinal cord stimulation of the thoracic and lumbar epidural space of patients with DPN has proven effective in relieving pain in extremely refractive patients. Neuropathic pain increases dramatically when the stimulator is turned off and pain relief returns when it is reactivated.

Acupuncture

Traditional acupuncture gives prolonged pain relief in up to 77% of patients with DPN. Most patients are able to reduce or stop other pain medication.

Surgery

Surgical decompression of nerves in the foot has been promoted as a treatment option for DPN. Although more than

240 surgeons have been trained in this technique in Europe, there is no evidence to support this therapy. This procedure will work when the pain is caused by a nerve entrapment but is definitely of no benefit in true DPN (see Fig. 3).

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Routine assessment by a health care professional/ podiatrist

It is of the utmost importance that every diabetic, newly diagnosed or long-standing, be assessed regularly by a trained podiatrist who is accredited as a 'dia-podiatrist'. This will not only be an economically sound policy of preventing foot problems before they happen, but will also enable patients to receive appropriate treatment from the start, before limb loss occurs. Risk stratification (Table I) is extremely important from the outset, and patient education and wearing the right footwear are all areas of expertise that trained podiatrists will offer their patients.

Table I. Risk categorisation system

Category	Risk profile	Check-up frequency
0	No sensory neuropathy	Once a year
1	Sensory neuropathy	Once every 6 months
2	Sensory neuropathy and signs of peripheral vascular disease and/or foot deformities	Once every 3 months
3	Previous ulcer	Once every 1 - 3 months

The American Diabetic Association has estimated that 50% of foot ulcers could be avoided if both the patient and the health care professional fulfil their respective responsibilities. Knowing that 85% of all amputations done in diabetics are preceded by foot ulceration, it is of paramount importance that ulcers are prevented. Foot deformities, callus formation and poorly fitting shoes are all aspects of DPN in the foot that need regular treatment and adjustment.

Conclusion

DPN has been labelled the 'forgotten complication of diabetes'. Although the clinical manifestations and treatment are far advanced in comparison with a decade ago, better methods to prevent the onset

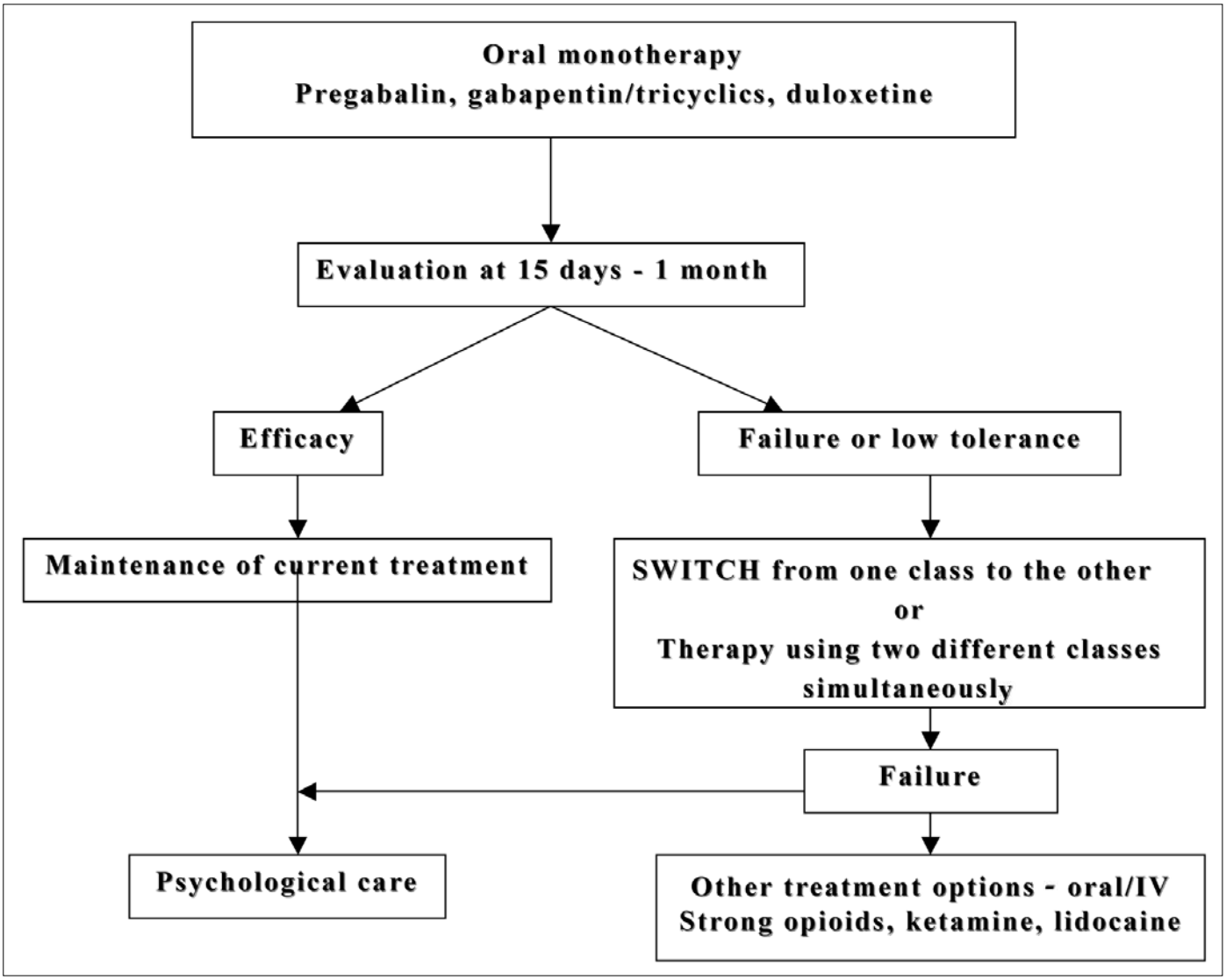

Fig. 3. Algorithm for the treatment of diabetic peripheral neuropathy. (Algorithm of the French Pain Society 2009 as presented by G Mick at the First Middle East Regional Diabetes Summit.)

and progression of the disease need to be researched.

If ulceration and amputation are to be avoided in the insensate foot, then clinician and patient education must be addressed as a matter of urgency. A stepwise treatment plan addressing all aspects of foot care, together with pharmacological control of severe neuropathic pain, will enable diabetic patients with DPN to have functionality and quality of life.

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Further reading

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In a nutshell

- Weight loss and depression are important manifestations of DPN.
- When treating DPN remember that you are managing a patient.
- Start medication slowly and in low doses.
- Explain potential side-effects to the patient at the first visit.
- Emphasise that complete relief of symptoms is rare and that a 50 - 75% improvement is considered substantial.
- If pain persists after 6 weeks of therapy, increase medication to maximal dose and add a second or even third medication to the regimen. Make sure that the patient is not smoking and check blood pressure, glucose and cholesterol.

Single Suture

More evidence against aspirin for primary prevention

In 1998, researchers in Scotland began a large trial of low-dose aspirin for adults without clinical cardiovascular disease. The results, now published, suggest that 100 mg of enteric-coated aspirin a day is no more effective than placebo at preventing serious vascular events including heart attacks, strokes and revascularisation procedures. These adults had an ankle brachial index below 0.95, indicating a higher risk of cardiovascular disease than the general population of Scotland. Even so, aspirin did not save lives during more than 8 years of follow-up, or protect participants from symptomatic disease. Aspirin caused significantly more major bleeds than placebo (1.71, 0.99 - 2.97), some of which were fatal.

The weight of evidence is now balanced against low-dose aspirin for primary prevention, says an editorial. This trial had its flaws, as most trials do, but if aspirin has any prophylactic effect in this population, it is likely to be small. The harms are more obvious. These researchers screened nearly 30 000 adults aged 50 - 75 to find the 4 914 with a reduced ankle brachial index. They managed to randomise 3 350. Around 70% of participants were women.

Gerald F, *et al. JAMA* 2010; 303: 841-848.