Diabetic Neuropathy: Clinical Features and Natural History

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SUMMARY

The clinical features of diabetes have been recognised over a thousand years ago. However the first description of diabetic neuropathy was by Rollo in 1798 when he described pain and paraesthesiae in the legs of a diabetic patient [1]. Pavy described a 'pain of a burning and unremitting nature' in 1887 [2], Diabetic neuropathy by causing an insensitive neuropathic foot causes considerable morbidity. In UK, 2% of all diabetic patients had active foot ulcers and 2.5% were amputees. Neuropathy is a significant cause of diabetic foot lesions [3].

The primary mechanism initiating nerve damage is hyperglycaemia. There is good evidence that achieving normoglycaemia can reduce the frequency of neuropathy. A diverse array of clinical presentation is possible as different nerve fibre populations may be affected in different manners. The acute neuropathies generally recover while the chronic neuropathies follow an insidious irreversible course. In research studies, at least one measure each from clinical symptoms, examinations, electrodiagnostic studies, quantitative sensory testing and when relevant, autonomic function testing should be performed in order to evaluate diabetic neuropathy. However, clinical examination alone may suffice for identification of the high risk foot in clinical practice. Therapy for painful neuropathy is with tricyclic antidepressants, phenytoin, carbamezapine and topical capsiacin. Diabetic neuropathy is a cause of significant morbidity in terms of amputations and prolonged hospitalisation. Early diagnosis and institution of appropriate preventive care can prevent many of these problems. This may include measures varying from simple foot care advice to provision of special footwear. Hence a multidisciplinary team approach to screening for neuropathy and preventing foot lesions is an essential component of any diabetes service.

Definition

Despite being considered one of the most common long-term complications of diabetes, detailed studies have been hampered by the lack of a uniform definition of diabetic neuropathy. The consensus of opinion at the San Antonio conference on diabetic neuropathy [4] was that diabetic neuropathy was " a descriptive term meaning a demonstrable disorder, either clinically evident or subclinical that occurs in a setting of diabetes mellitus without other causes of neuropathy. The neuropathic disorder includes manifestations in both somatic and/or autonomic parts of the nervous system."

Classification

A classification of neuropathy in a diabetic patient should be acceptable from a clinical and pathological aspect. However, the lack of knowledge about aetiology and pathogenesis of diabetic neuropathy has led to a variety of classifications. Clinicians often use a simple clinical classification [5] (Table 1).

Table 1

Clinical subdivision of the diabetic neuropathies

Mononeuropathies	**Polyneuropathies**
Cranial	Sensory
Proximal motor	Acute sensory
Isolated peripheral	Autonomic
Mononeuritis multiplex	Painful neuropathy
Radiculopathy (Truncal neuropathy)	

Clinical Features

Mononeuropathies

Most forms of mononeuropathy are more common in diabetic patients compared with nondiabetics, but remain relatively rare in comparison with the polyneuropathies [6].

Proximal motor neuropathy

This relatively uncommon neuropathy, previously known as 'amyotrophy', is most often seen in older patients with NIDDM particularly males, is unrelated to duration of diabetes and may be a presenting feature of diabetes [7]. Patients present with pain and weakness with or without wasting in the proximal muscles of the lower limbs, often with asymmetric involvement. It is often bilateral with the second side becoming affected simultaneously or within one to two weeks. The knee jerk is absent and the ankle jerk is present. Weakness of the proximal muscles makes climbing stairs impossible.

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It is imperative that other causes of nerve root compression are excluded before reaching a diagnosis. The prognosis for this condition is generally good, with gradual recovery following no specific therapy other than control of diabetes [8].

Cranial neuropathies

Cranial nerve palsies affecting the occulomotor and abduscens nerve are associated with diabetes. The onset is abrupt and is usually a 'medical' third nerve palsy with sparing of the pupils. Ptosis may be absent. The condition is more common in men and may relapse. [9]

Radiculopathies

Radiculopathy can affect any nerve root. It most commonly affects the trunk. It is characterised by pain, often severe. A characteristic physical sign of bulging of the abdominal wall may be seen frequently, The condition is self limiting with complete resolution within one to three years [9].

Autonomic neuropathies

These may affect any tissues receiving autonomic innervation but fortunately symptoms of autonomic neuropathy, which may be severely disabling, are relatively infrequent [10], However, objective evidence of dysfunction is frequently found in diabetic subjects, and is sometimes seen even at diagnosis [10,11].

Painful neuropathy

Varying degrees of pain may be felt by patients with diabetic neuropathy. This may range in severity from paraesthesiae to excruciating and disabling pain. Pain may be a feature of proximal motor neuropathy or truncal radiculopathy. There is a poor correlation between physical signs and symptoms. Some patients may have a complete anaesthesia to pin prick but have severe pain. This has been described as the 'painful painless leg [12]. The pain is usually persistent. Paraesthesiae, constant burning pain and shooting or searing pains have been described. Hyperaesthaesiae or contact discomfort has been reported by such patients. Patients may be unable to stand contact of socks and bedclothes.

Painful neuropathy can occur at any age and is not associated with duration of diabetes. However achieving good control in poorly controlled patients especially with initiation of insulin therapy may be associated with a painful neuropathy [3]. It has been suggested that painful neuropathy is caused by selective involvement of small nerve fibres. However recent studies have failed to identify functional differences in different nerve fibre populations [13].

Clinical and electrophysiological recovery from painful neuropathy is usually the rule. It may take upto one year for symptoms to disappear. Weight loss may be associated with painful neurcpathy. This has been previously described as 'diabetic neuropathic cachexia'. However recovery from pain is invariably followed by returning to normal weight [14]. Patients with painful neuropathy do not necessarily progress into a sensorimotor neuropathy but some patients may be troubled by mild painful symptoms.

Polyneuropathy

The most frequent peripheral nerve disorder in diabetes is a symmetrical polyneuropathy involving predominantly the lower limbs. Over two thirds of patients may have this form of neuropathy [15]. These disorders develop insidiously over many years and are directly related to the duration of diabetes. However not all diabetic patients develop neuropathy.

It is possible to identify two main subtypes of the sensory neuropathies. The acute sensory polyneuropathy is characterised by a relatively rapid onset of symptoms that are often particularly severe, with constant burning discomfort and paraesthesiae (all with marked nocturnal exacerbation) being the most troublesome [16, 17]. These symptoms are often accompanied by weight loss, but often occur without many objective physical signs. In contrast, in the more common chronic sensorimotor neuropathy, symptoms are of insidious onset and may be positive (burning pain and sharp, stabbing or shooting sensations) or negative (numbness, feet feel 'dead') depending on the type of nerve fibre involved [3-17]. A stocking and glove sensory loss is usually found on examination, together with small muscle wasting and absent ankle reflexes.

There is a great deal of conflicting evidence in the literature on the prevalence of diabetic neuropathy (18). The absence of definitive criteria may explain this. If only abnormalities of nerve conduction velocity were accepted as definitive evidence of neuropathy, the prevalance would be 100%. This problem is further complicated by the fact that the prevalence of neuropathy increases with age, duration of diabetes and glycaemic control [19]. However, with the use of more rigorous criteria, including symptoms for at least one year, clinically evident abnormalities and electrophysiology, the

prevalence in an average clinic population of insulin-treated patients is reported to be 10-15% [20, 21]. It is likely that at least one third of diabetic patients will have some clinical evidence of peripheral neuropathy. In patients with other diabetic complications, the prevalence will be higher [20]. The prevalence in a UK clinic population was estimated to be 28.5% [22] and 27% in a Sri Lankan clinic [23].

Assessing the natural history and prognosis of diabetic neuropathy is affected by several factors. Different nerve fibres may be affected at different rates. Small nerve fibres whether myelinated or unmyelinated are affected first in diabetic neuropathy. Consequently it is common to find patients presenting with diminished thermal sensation, while large fibre modalities are normal (i.e. vibration perception and joint position sense) [24].

The prognosis for acute sensory neuropathies is good, with complete recovery occurring in most cases within a few months [16, 17]. However the chronic sensorimotor neuropathy has a less favourable prognosis. Many patients suffer from intermittent symptoms for several years [25]. In contrast to acute sensory neuropathy, symptoms of chronic sensorimotor neuropathy are of insidious onset and may persist for years. A gradual improvement of painful symptoms does not necessarily indicate structural improvernent. There may be a further loss of small fibre function, leaving the patient with a numb, insensitive foot that is at risk of painless injury [26].

The variable natural history of diabetic neuropathy, its variability with age and duration of diabetes and its diverse clinical presentations leads to some difficulty in devising methods of diagnosis and quantification.

The consensus statement released by a panel of neurologists and diabetologists in 1988 is useful in standardising diagnostic criteria for research purposes. At least one measure each from clinical symptoms, examinations, electrodiagnostic studies, quantitative sensory testing and when relevant, autonomic function testing should be performed in order to evaluate diabetic neuropathy [4].

Assessment of Neuropathy

Clinical Symptoms

Although symptomatic assessment is subjective, the symptoms are the primary reason for a medical consultation. The patients will judge the success of any intervention on its ability to relieve symptoms. Neuropathic pain may consist of a number of uncomfortable sensations experienced by the patient. Pain is a subjective experience, and there is marked variation in its perception between patients and consequently their description of the symptom. Yet the evaluation of subjective complaints is often considered an important component of the clinical assessment. Symptoms should be evaluated by the patients, perception of their severity. They must be recordedas described by the patient and medical jargon should not be substituted in place of the patient's description of symptoms.

Differing approaches have been used for the assessment of symptoms in research studies. One commonly used system scores symptoms on a visual analogue scale [27]. A neuropathy symptom score derived from history may be used instead [28]. Symptoms may have characteristic qualities other than their severity or intensity. Patients may choose from among a variety of descriptions, the one that best describes their own symptom [29]. This questionnaire may be useful in symptom assessment and discrimination in diabetic neuropathy [29].

Clinical Examination

The routine neurological examination is useful in clinical practice [30]. However it lacks precision and is not objective or reproducable. Hence it is of little use in clinical trials. As with symptoms, neurologic deficit scores calculated from the examination are useful as the information obtained may not be available through other tests [31]. A careful clinical assessment will also help to exclude alternative causes of symptoms such as significant peripheral vascular disease [31]. Reduction or absence of large and small fibre function in a glove and stocking distribution, with reduced reflexes are common findings in sensorimotor neuropathy. In research the reliability and reproducibility of clinical findings can be improved by reporting reflexes as present or absent rather than using vague variable terms such as 'reduced' or 'weak'. This will give an objective score from which a neurological disability score may be derived [31]. This is achieved by scoring deficits from selected items in the neurologic assessment and then calculating the final total score.

The following caveats must be borne in mind when interpreting clinical examination. Ankle reflexes may be absent in the elderly and vibration perception is poor in elderly patients. Hence age-matched normal data should be available for

comparison when interpreting clinical scores. The sensory deficit may be a very patchy and a normal neurologic examination does not necessarily exclude the presence of a significant sensory neuropathy.

Electrophysiological Studies

Electrophysiological measures of nerve function have been the mainstay of 'objective' assessment of neurological deficits in diabetic patients [3]. Some form of abnormality can be detected in the majority of patients. Symptoms do not necessarily correlate with the electrophysiological abnormalities [32]. Abnormal results of a nerve conduction study are not specific for aetiology. The abnormality may be caused by another cause such as alcohol. Errors in measurement of nerve-conduction velocities may arise when temperature of the measured appendage varies between measurements or in different subjects. Calculation of conduction velocity depends on accurate measurement of distance between sites of stimulation. This is done with a tape measure. Errors may occur at this stage. With meticulous attention to technique and detail, despite these limitations electrophysiological studies provide useful information on nerve function.

The analysis of action-potential amplitude relates to the total number of active fibres, whereas conduction studies reflect the functional status of the large myelinated motor and sensory fibres. In research the F-response and the Hoffmann[H] reflex may also provide information of value [33, 34]. The results of multiple electrophysiological tests of nerve function may be combined to give a 'soore' of neurophysiologic dysfunction. As with symptoms and examination, such a composite score may be useful in longitudinal studies of natural history or to assess pharmacological intervention in diabetic neuropathy.

Quantitative Sensory Testing

Tests of somatosensory function evaluate sensations evoked by stimulation of cutaneous receptors. They depend upon a subjective sensation of the patient. These sensitive techniques record early abnormalities in diabetic neuropathy. Hence the Consensus conference on diabetic neuropathy strongly recommended their use in clinical trials and epidemiological studies.

Thermal sensation is a small-fibre function. The Consensus conference recommended methods that employ a forced choice paradigm. These methods are reproducable and detect early sensory abnormalities [35]. The reduction of thermal sensation may be the only abnormality in painful neuropathy [36].

Vibration perception is a test of large fibre-function. The biothesiometer (Biomedical Instruments Co, Newbury, Ohio) is the most commonly used instrument. A combination of thermal and vibration testing is recommended in the screening of patients being considered for clinical trials.

Current Perception Threshold

The neurometer is a device for assessment of peripheral nerve function that assesses current perception threshold [37]. It is a constant current sine wave generator that appears to test different nerve fibre populations.

Pressure Perception Threshold

The ability to sense pressure may also be used as an index of peripheral nerve function. The Semmes Weinstein Monofilaments consists of a series of nylon filaments that buckle under a specific pressure. When pressed on to the limb tested a pressure perception threshold may be assessed.

This method is economical and well within the reach of South Asian practitioners and clinics as it costs around US $ 15 compared to the US $ 1700 for a biothesiometer and US $ 12,000 for a neurometer [38].

Prevention and Management of Neuropathy

The exact pathophysiological mechanism by which nerves are damaged in diabetic neuropathy is controversial and a subject of debate, but prolonged hyperglycaemia is an accepted primary causative mechanism [39]. The Diabetes Control and Complications Trial (DCCT) showed conclusively that intensive glycaemic control decreased the occurrence of diabetic neuropathy [40]. Hence good glycaemic control is a measure for primary prevention of neuropathy. Aldose reductase inhibitors have shown limited benefit but are not recommended for routine clinical practice [39].

Therapy for painful neuropathy is with tricyclic antidepressants, phenytoin, carbamezapine and topical capsiacin [41 , 42]. Amitryptiline in doses of 25 mg at bedtime to a maximum of 150 mg daily have been found effective. Topical capsiacin, an ingredient of pepper has been used. It acts by depleting the pain modulator P from sensory

neurones. It has shown in a double blind clinical trial to reduce intensity of pain.

The neuropathic foot is a significant cause of mortality and morbidity. It leads to frequent and prolonged admission of patients with diabetic foot lesions. The neuropathic foot is a common cause of amputation in both developed and developing countries [39]. As many as 50% of these amputations can be prevented. A policy of screening to identify high risk feet and initiation of appropriate treatment is recommended.

Careful clinical examination is sufficient to identify a high risk foot and this may even be performed in economically deprived settings. However, quantitative sensory testing will give additional information on severity of the neuropathy. Patients known to have high risk neuropathic feet should be targetted for foot care advice. The provision of special services for such patients has been shown to reduce the number of amputations among patients with high risk feet [43, 44].

Diabetic neuropathy is a cause of significant morbidity in terms of amputations and prolonged hospitalisation. Early diagnosis and institution of appropriate preventive care can prevent many of these problems. This may include measures varying from simple foot care advice to provision of special footwear. Hence a multidisciplinary team approach to screening for neuropathy and preventing foot lesions is an essential component of any diabetes service [45].

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