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REVIEW

Diabetic Neuropathy

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Abstract

The diabetic polyneuropathy (DN) is a common disorder with diverse clinical presentations depending on the type and duration of diabetes, number of nerve fibers affected and its glycemic control. They progress in length-dependent pattern causing severe sensory-motor deficit, more common in distal lower limbs than in upper limbs. In addition, small fiber polyneuropathy has been identified in vast majority of patients affecting sensory and autonomic system in distal limbs. Excruciating pain, trophic changes in the feet, abnormal sweating and numbness are the main manifestations of small fiber DN. Occasionally diabetic neuropathy can present with focal and multifocal neuropathies of cranial, truncal and peripheral nerves among patients with long standing diabetes and age over 50. The length dependent DN hardly improves over period of time when compared to focal or multifocal neuropathy which is usually self-limiting after a course of few relapses. Therefore, adequate attention should be paid on early clinical diagnosis, identifying sub types and complications to tailor the appropriate treatment or to initiate preventive measures to avoid the devastating consequences of DN.

Introduction

Diabetes is one of the oldest known diseases, well recognized for over thousands of years. However, pain and paresthesia as clinical features of diabetic polyneuropathy (DN) were first described by Rollo in 1798 [1]. Patients with DN may present with multiple neurological problems involving somatic (proximal/distal) and autonomic nerves, often affecting legs and feet. It has recently been identified as an emerging problem in the developing countries including Sri Lanka contributing to substantial morbidity and mortality leading to huge economic burden. DN may be silent and go undiagnosed while its effects are being experienced by the patients. Also the DN is a significant cause of diabetic foot lesions[2]. Thus, the physicians need to be vigilant in managing diabetic patients and should always be aware of the symptoms that help in early identification to initiate the appropriate management of DN.

Clinical features

The diversity in clinical presentations of DN depends on the types, number and anatomical pattern of nerve fibers affected and the duration of illness (Table 1)[3]. Nonetheless, serious and the most common type of nerve injury is primarily caused by sustained high blood glucose in long-standing diabetics, 15 -20 years, after initial diagnosis regardless of its types[4]. Further, the DN counts 75% of neuropathy and thus it is mainly focused in the review[5]. Other recognizable pattern of DN are diabetic

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autonomic neuropathy, cranial neuropathy, mononeuritis multiplex, mononeuropathies, radiculoplexopathies, diabetic neuropathic cachexia, hyperglycemic polyneuropathy and treatment induced- neuropathies[6]. The main fiber types in DN and their symptoms are given in table 2. It is noted that between 30 -50% of patients with long standing diabetes might have one or multiple forms of these nerve problems in their life time[7,8]. In contrast, mononeuropathies related to pressure palsies such as carpal tunnel syndrome, Ulnar nerve palsies and common peroneal nerve palsies, are not very specific to diabetes. These spectrum of diabetic neuropathic syndrome have distinguishing pathophysiological, therapeutic and prognostic features. The table 3 gives further information on mono neuropathy, entrapment neuropathy and polyneuropathy. The table 4 compares two major types of diabetic neuropathy which affect predominantly the motor nerves of the limbs such as diabetic amyotrophy and chronic inflammatory demyelinating polyneuropathy. (CIDP).

Symmetric neuropathies
Diabetic polyneuropathy
Diabetic autonomic neuropathy
Neuropathy with impaired glucose tolerance
Painful sensory neuropathy with weight loss (diabetic cachexia)
Insulin neuritis
Hypoglycemic neuropathy
Polyneuropathy after ketoacidosis
CIDP in Diabetes
Asymmetric neuropathies
Diabetic cranial neuropathy
Diabetic Mononeuropathies
Median Neuropathy at wrist
Ulnar neuropathy at elbow
Peroneal neuropathy at head of fibular
Radiculoplexus neuropathies
CIDP = chronic inflammatory demyelinating polyradiculoneuropathy
DLRPN = diabetic lumbosacral radiculoplexus neuropathy
DTRN=diabetic thoracic radiculoneuropathy
DCRPN=diabetic cervical radiculoplexus neuropathy

Table 1: Diabetic neuropathy depending on type, number and anatomical pattern of nerve fibers

Natural history of diabetic neuropathies

Natural progression of DN primarily depends on the glycemic control and the duration of type 1 and type 2 diabetes mellitus. In type 1 diabetes mellitus, the most common presentation is an initial rapid deterioration of nerve conduction studies followed by a slow phase of 2-3 years[9]. Whereas in type 2 diabetes slow nerve conduction study may be the only earliest sign at the time of diagnosis. In both type 1 and 2 diabetes mellitus, the progression of the DN is steadily concordance with the duration of illness. Furthermore, patients with symptomatic DN generally have slow conduction velocities than asymptomatic[9]. However, on long term follow up, Type 2 than type 1 diabetes mellitus shows remarkable loss of CMAP. Amputations and prolonged hospitalization are the major morbidities of untreated DN.

Toronto Consensus Panel on Diabetic Neuropathy has defined diabetic neuropathy

as a "symmetrical, length – dependent sensory- motor polyneuropathy attributable to metabolic and microvascular alterations as a result of chronic hyperglycemic exposure and cardiovascular risk covariates" [10]. A range of initial sensory symptoms such as loss of pain sensation, tingling sensation, "pins and needle", burning pain, electric shock like feeling, painful sensation to minor stimulation (allodynia) and increased sensitivity to a light pain stimulation (hyperalgesia), have also been reported in DN[11]. These symptoms usually affect toes and, on progression of the illness, spread to legs (below knee and sometimes above knees) before getting involved the hands. This is called as length dependent sensory- motor neuropathy. In most of the instances these symptoms of DN leave untreated by the patients unless the neuralgic pain disturbs their sleep or quality of life. A few literature review estimated that only 20 – 30 % of patients with DN had such debilitating neuropathic pain necessitated medical attention to get rid off their pain[12].

Pathogenesis

The pathogenesis of DN is incompletely understood. Therefore the current treatment regimens are unsatisfactorily to meet the need for effective treatment of DN. However, according to a landmark Diabetic Control and Complication Trial (DCCT), hyperglycemia had shown to be the key independent risk factor for DN. This could be due to a persistent hyperglycemia causing microvasculopathy

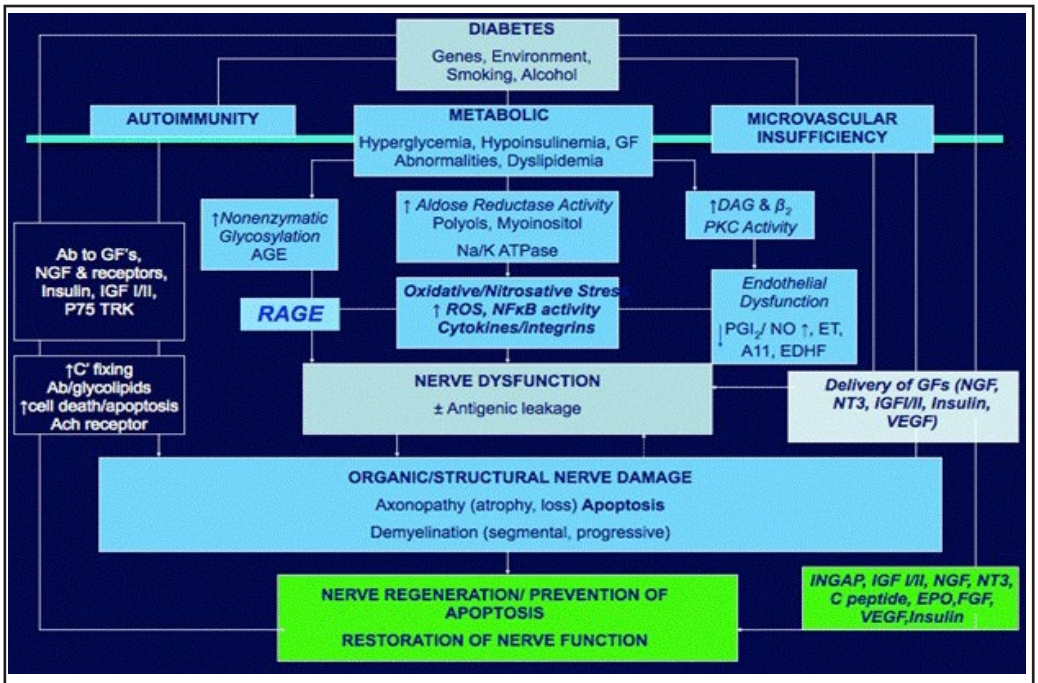

Figure 1 : Pathogenesis of diabetic neuropathies

Ab-antibody; AGE-advance glycation end products; C– complement; DAG -diacylglycerol; ET- endothelin; EDHF- endothelium-derived hyperpolarizing factor; GF- growth factor; IGF- insulin-like growth factor; NFkB - nuclear factor kB; NGF - nerve growth factor; NO - nitric oxide; NT3 - neurotropin 3; PKC - protein kinase C; PGI2 -prostaglandin I2; ROS - reactive oxygen species; TRK - tyrosine kinase.

Diabetic neuropathies	Nerve affected	Symptoms
Sensory neuropathy Distal neuropathy Femoral neuropathy	Sensory	Pain Numbness/ tingling Loss of sensation
Autonomic neuropathy	Autonomic	Impotence Bladder dysfunction Diabetic diarrhea Gastroparesis Postural hypotension Charcot's joint
Motor Neuropathy Diabetic amyotrophy	Motor	Muscle weakness

Table 2 : Polyneuropathy and symptoms of affected nerves

leading to DN. This study also shed some light on the underlying molecular events driven by hyperglycemia, which cannot be rectified by the subsequent control of blood glucose levels called "metabolic memory"[13]. Other proposed causative factors include oxidative and nitrosative stress, defective neurotrophism, and autoimmune-mediated nerve destruction as shown in Figure 1[14]. Further, microvascular defects was the pathological characteristic change identified among patients with DN in sural nerves biopsies, but not in diabetics without DN.

Features	Mononeuropathy	Entrapment Neuropathy	Polyneuropathy
Onset	Sudden	Gradual	Gradual
Pattern	Single nerve / painful (many individual nerves affected is called as Mono neuritis multiplex)	Single nerve and minor trauma	Distal symmetrical, usually Length dependent poly neuropathy
Nerves affected	CN: III, VI and VII PN: median, Ulnar, Radial, peroneal, lateral and medial plantar nerves.	PN: median, Ulnar, peroneal, lateral and medial plantar nerves	Mixed, Motor, Sensory, Autonomic
Natural history	Resolve spontaneously	Progressive	Progressive
Treatment	Symptomatic	Rest, splints, local steroids, diuretics or surgery	Tight Glycemic control, Pregabalin, Duloxetine, Antioxidants
Distribution of sensory loss	Concordance with the nerve innervating the area	Area distal to the site of entrapment	Distal and symmetrical. "Glove and Stocking" distribution

Table 3 : Comparison between Mononeuropathy, Entrapment Neuropathy and Polyneuropathy

Diagnosis of Diabetic neuropathy

It is primarily a clinical diagnosis based on relevant history and confirmatory examination findings associated with neuropathy. The neuropathic pain, either intermittent or continuous, affects more at night. It is described as burning, stubbing, tingling, numb, hot or cold extending distal to proximal in "glove and stocking" distribution. Various validated neuropathic pain scales have been devised to aid the diagnosis and assess the severity of illness.

The large fiber deficit can be evaluated by checking deep tendon reflexes, pin prick sensation and monofilament examination. In contrast, there is no reliable tool available to assess the small fiber deficits.

There are a few emerging markers such as nerve biopsy and intraepidermal nerve fibers (IENF) for small fiber DN proposed with some validated measures. In which the nerve biopsy of an early DN reveals damages in unmyelinated fibers, while preserving myelinated fibers[20]. Further a morphometric quantification of IENF is a reliable and efficient technique to confirm the clinical diagnosis of small fiber DN with 77.2% and 79.6% sensitivity and specificity respectively in a study group. [21]

Features	Diabetic amyotrophy	CIDP
Age	50 – 60 years	50 – 60 years or younger adults
Onset	Gradual / abrupt	Gradual
Distribution	Proximal	Proximal> distal
Pain	Severe pain in thighs, hips and buttocks associated with proximal weakness / wasting	Usually painless
Unilateral / Bilateral	Usually unilateral; can affect asymmetrically both thighs. Can have co-existing polyneuropathy	Usually bilateral
NCS / EMG	Axonal neuropathy , spontaneous or provoked fasciculation	Demyelinating neuropathy,
Treatment	Intravenous steroids	Intravenous steroids / immunoglobulin/ Plasmaparesis

Table 4 : Comparison between diabetic amyotrophy and CIDP

Management

Management of DN is a multidisciplinary approach including symptomatic treatments of DN and controlling major vascular risk factors related to diabetes.

Preventive measures

Primary preventive measures of DN includes implementation of intensive glycemic control to reduce the occurrence of DN; based on the landmark trials in type 1 DM - the Diabetes Control and Complications Trial (DCCT). For many years it had been assumed that the same was true in DN related to type 2 diabetes as well. However, recent multiple studies have proven that there is no meaningful impact on risk reduction related to DN with aggressive versus standard glycemic control[15]. Further, some small studies related to metabolic syndrome suggest that diet and exercise may slow down the progression of DN by promoting small nerve fiber regeneration in pre diabetic and diabetic patients[16]. The main aim of management in DN is to prevent diabetic complications including diabetic foot ulcers and falls. Lifetime risk of developing diabetic foot ulcers for a diabetic patient is 15.2%. This can be reduced by modifying various metabolic factors contributing to diabetes, in addition to, educating patients about the essential of using footwear, periodic foot examinations and podiatric care for high risk foot. The second major complications of DN is a high risk of fall. Patients with DN have three times increased risk of fall compared with diabetes without DN. However, in many of the instances, it had been under- reported by the patients or caregivers. Therefore, primary prevention should be started with the help of primary care providers to assess the risk of fall, to arrange health education as well as to make arrangements for physiotherapy or community exercise program when appropriate[22]. In secondary prevention, measures should be taken for early diagnosis of DN and institution of appropriate preventive care such as advice on foot care or provision of special footwear. Hence these multilevel clinical approaches would definitely help to prevent such common dreadful situations in diabetes.

Symptomatic treatment

Pain in DN is usually associated with polyneuropathy, except at rare occasions of acute painful DN, presenting with neurological signs[17]. The treatment response in painful DN can be evaluated by various validated tools while treating patients with medications. Visual analogue scale is the oldest and the best validated tool for assessing the severity of pain reliably[17]. Concurrently, a validated neuropathy-specific scale can also be used to assess the overall treatment outcome[17]. Level 1 evidence support, the use of tricyclic antidepressant (Amitriptyline), gabapentin, pregabalin, oxycodone, tramadol and Duloxetine in painful DN. In addition the use of topical treatment, 5 % lignocaine plaster, also gives some promising effect[19].

Cardiac autonomic neuropathy (CAN) is significantly associated with cardiac mortality. Thus screening for CAN should be done at the time of diagnosis in all patients with type 2 diabetes and at 5 years in type 1.

Pathogenic treatment

The only newly emerged anti- oxidant recommended to treat DN is intravenous

α-lipoic acid. This agent modifies various steps in metabolic pathways leading to DN. (Level 1 evidence)[18].

Moreover, the management of DN and related supportive management is relatively expensive. This is supported by a recent cost comparison study for the management of pain. It revealed that the cost of Pregabalin at its initial dosage for one month and the same for Duloxetine were $189.98 and $170.99 respectively which were compared with gabapentin ($ 18.99) and amitriptyline ($ 12.99)[23]. Moreover, the management cost of foot ulcers and its complications were too expensive. Patients with DN had 15% risk of getting diabetic ulcer and 6 – 43% of them eventually needed amputation of one or both limbs in their lifetime[11,24]. Therefore, this isolated illness per se can cause major economic crisis to a country.

Conclusion

DN is one of the major disorders causing long term morbidities in diabetes. The diagnostic criteria, pathogenesis and treatment of DN have yet to be defined. Therefore, there is a clear need for research and periodic updates by experts from this challenging field.

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