International Journal of Medical and Health Research
ISSN: 2454-9142, Impact Factor: RJIF 5.54
www.medicalsciencejournal.com
Volume 2; Issue 11; November 2016; Page No. 29-33

Diabetes-associated peripheral neuropathies

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Abstract
Objective: To describe the various peripheral neuropathies of diabetes mellitus.
Methods: A Pubmed search of the English-language literature using a combination of words (diabetic neuropathy, diagnosis,) was used to identify original studies, consensus statements, and reviews published in the last thirty years.
Results: The diverse neuropathies of diabetes mellitus seen in clinical practice.
Conclusion: Prompt diagnosis and recognition of these with the institution of appropriate treatment measures would go a long way towards reducing morbidity and mortality outcomes.

Keywords: Diabetes, peripheral, neuropathies

Introduction

Diabetic peripheral neuropathy is defined as the presence of symptoms and signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes [1]. It manifests in the somatic, sensory and or autonomic parts of the peripheral nervous system [2, 3]. The sensory phenotype is divided into: small, large or mixed fiber types [4]. Symptoms of neuropathy are very common, and subclinical neuropathy is more common than clinical neuropathy [5]. Neuropathy may remain undetected, and progress over time leading to serious complications.

With the rising global burden of diabetes, peripheral neuropathy, and other diabetes complications are expected to be on the increase [6]. This would negatively affect their quality of life and mortality. The most common clinical presentation of diabetic peripheral neuropathy is distal symmetrical polyneuropathy [7].

This review focuses on the common neuropathies encountered in clinical practice. We also bring to fore the rarely thought about neuropathies commonly misdiagnosed as other conditions. A good knowledge of these neuropathies would go a long way in improving the patient care offered by the diabetes clinician.

Anatomic considerations

Small fiber neuropathies manifest with painful paresthesias most commonly over the lower limb. The pain may be dull, aching, burning, lancinating or cramp-like. Paresthesias may manifest as a sensation of coldness, numbness or tingling. There may be associated diminution of pain and temperature perception in the lower limbs in a glove and stocking distribution. Features of large fiber neuropathy include loss of ankle jerk, impaired position, and vibration sense, sensory ataxia [8]. Mixed small and large fiber neuropathy is the most common variety of painful diabetic neuropathy.

Table 1: the neuropathies of diabetes mellitus

Acute painful neuropathy
Chronic sensorimotor distal symmetrical polyneuropathy
Painful small fiber neuropathy
Diabetic neuropathic cachexia
Focal limb neuropathies
Compression neuropathies
Cranial neuropathies
Diabetic amyotrophy
Diabetic truncal radiculoneuropathy
Chronic inflammatory demyelinating polyneuropathy associated with diabetes Insulin neuritis
Rapidly reversible hyperglycaemic neuropathy
Hypoglycaemic neuropathy
Impaired glucose tolerance neuropathy
Diabetic autonomic neuropathy

Acute painful neuropathy

First described by Archer *et al.* [9] in 1983, is a distinct and common variant of distal symmetrical polyneuropathy that presents with abrupt onset of severe sensory symptoms with little or no sensory and motor signs. It usually follows a period of change in glycemic control [10]. It usually starts with rapid weight loss over a short period followed by severe, unremitting pain mostly in the feet. Optimizing glycaemic control eventually leads to weight gain and remission of symptoms.

Chronic sensorimotor distal symmetrical polyneuropathy

Chronic sensorimotor distal symmetrical polyneuropathy (DSPN) is the most common form of diabetic neuropathy. It is present in more than 10% of patients at the diagnosis of type 2 diabetes with an insidious onset. More than 80% of patients with clinical diabetic neuropathy have a distal symmetrical form of the disorder [11].

Symptoms may be positive or negative. Positive symptoms include feelings of pins and needles, tingling, burning, and neuropathic pain. Negative symptoms include numbness, impaired tactile, thermal and pain sensation. Positive symptoms, probably due to neural hyperexcitability, include

pins and needles and pain which may be of varying qualities (burning, aching or lancinating). These negative and positive sensory symptoms may coexist

Symptoms begin distally in the toes and the feet and gradually extend proximally to involve the hands and fingers [12]. This pattern of spread or progression reflects the dying-back nature of underlying nerve damage [13]. Unsteady gait can be the result of sensory loss with or without concomitant weakness. Although this chronic neuropathy is related to the duration and severity of hyperglycemia, it can occasionally be the presenting symptom of occult diabetes mellitus. Significant sensorimotor and autonomic abnormalities may occur in patients with mild degrees of hyperglycemia. The first sign is a loss of vibration sensation in the feet followed by loss of ankle reflexes. Investigation for other causes of neuropathy usually yields a normal result.

Painful small fiber neuropathy

It is a variant of distal sensorimotor polyneuropathy in which the small myelinated fibers are affected alone or out of proportion to large nerve fibers [14]. Key complaints are burning or stabbing pain in the feet which may be spontaneous [15]. This form of neuropathy is usually distressing and debilitating, impairing patients' quality of life.

Diabetic neuropathic cachexia

It was first described by Ellenberg [16] in 1974. It is characterized by extreme weight loss and neuropathic pain. Patients are typically males in the sixth decade with simultaneous onset of diabetes and bilateral symmetrical peripheral neuropathy, anorexia, impotence, absence of other specific complications. The weight loss usually exceeds more than 50% of original body weight and usually occurs spontaneously due to uncontrolled diabetes. The response to the institution of good glycaemic control, tricyclic anti-depressants, and pregabalin is good [17, 18]. Complete resolution of these neuropathic symptoms is usually the rule, occurring within a period of over 6 to 24 months.

Focal limb neuropathies

Most persons with diabetes and upper limb neuropathic symptoms and signs will either have a mononeuropathy or multiple mononeuropathies [19]. This adds to the disability already imposed by the polyneuropathy that is almost always present. Ulnar neuropathies in people with diabetes are often insidious and are mainly motor with limited sensory symptoms and signs. Such focal neuropathies can easily go undetected because their symptoms are thought to be due to a polyneuropathy [20]. When sensory or motor symptoms are more prominent in the hands than feet, carpal tunnel syndromes or ulnar neuropathies should be suspected and excluded.

Cranial neuropathies (diabetic ophthalmoplegia)

Oculomotor nerve palsies are the most common cranial neuropathy observed in diabetic patients [21]. It occurs in rarely occurs in children. It affects mostly middle age adults. The pupillary function is spared. It has been attributed to ischemia occurring centrally within the third nerve, preserving the peripherally located parasympathetic pupil-constrictor fibers. This is in contrast to compressive lesions of the oculomotor nerve, such as an aneurysm of the posterior communicating artery, in which the pupillary fibers are affected [22]. Sixth nerve palsies also occur, but rarely. It is unclear whether seventh nerve palsies occur more frequently in people with diabetes than in the general population.

Compression neuropathies

Compression or entrapment neuropathies are more common in people with diabetes. They include carpal tunnel syndrome (CTS), ulnar neuropathy at the elbow (UNE), meralgia paraesthetica (entrapment of the lateral femoral cutaneous nerve of the thigh) at the inguinal ligament or peroneal neuropathy at the fibular head [22]. Nerve conduction studies should be carried to conform compressive median or ulnar mononeuropathies and to screen for associated axonal injury. Those found to have pure demyelinating neuropathy usually respond well to positional splints while those with active demyelination are treated with carpal tunnel decompression which as nearly as effective for diabetic patients as for normoglycemic controls [24].

Diabetic truncal radiculoneuropathy

It occurs in the setting of long-standing diabetes with other complications, especially polyneuropathy. Most of the affected individuals are in the 5th or 6th decade of life with a variable duration of diabetes [25]. It presents gradually with painful paresthesias in variable size patches unilaterally or bilaterally in the lower anterior chest or upper abdomen with nocturnal worsening. Associated involvement of motor nerve fibers can lead to bulging of the abdominal wall in the paraesthetic areas, best appreciated when the patient is standing [26]. Examination usually reveals a patch of sensory anomaly in the region of the symptoms [27, 28]. A thorough examination of the thorax and abdomen is necessary for a diabetic person presenting with unexplained thoracoabdominal pain. It resolves, spontaneously within 2-6 months.

Diabetic amyotrophy

This condition goes by a bewildering variety of names: proximal diabetic neuropathy, diabetic lumbosacral plexopathy, diabetic polyradiculopathy, proximal diabetic neuropathy, ischemic proximal mononeuropathy multiplex associated with diabetes mellitus, Bruns-Garland syndrome, and diabetic lumbosacral radiculoplexus neuropathy [29, 30].

It is commonly seen in males and type 2 DM with sudden or gradual onset. Neuropathic pain is severe and a prominent feature, Motor features include weakness of the proximal leg and hip girdle. The quadriceps is wasted and is the most commonly affected muscle. Affected persons find it difficult to stand or walk. All these symptoms and signs are usually, but not always, asymmetrical. Patients frequently have coexisting sensorimotor polyneuropathy [31]. Extensive investigations are not necessary.

Chronic inflammatory demyelinating polyneuropathy associated with diabetes

Patients with DM seem to develop clinical and electrophysiologic characteristics in keeping with CIDP. This condition tends to occur more frequently in people with diabetes than in non-diabetics. The rapid onset and progression of the neuropathy, demyelinating features on nerve conduction studies and an excellent response to

immunomodulatory treatments distinguish this entity from the far more frequent chronic diabetic sensorimotor polyneuropathy [32]. Treatment should be instituted promptly to prevent ongoing demyelination and the secondary axonal loss that would result in permanent disability [33].

Insulin neuritis

It is a distinct variant of distal polyneuropathy presenting with neuropathic symptoms, autonomic symptoms or both in patients who attain rapid glycemia after a long period of poor control [34]. Carvati described it [35] in 1933. It is also known as treatment related neuropathy or neuropathy after the onset of insulin use. The pain usually affects the feet and is mostly nocturnal [36]. Though its pathogenesis is poorly understood, some proposed mechanisms include regenerative nerve firing, hypoglycemia induced endoneurial firing and neuronal ischemia [37].

Signs are usually absent with relatively normal findings on clinical examination, except for allodynia (exaggerated response to non-painful stimuli) and, occasionally, absent or reduced ankle reflexes. Usually, it occurs in the setting of rapid weight loss after the commencement of medication to control glucose. It primarily occurs in people with type 2 diabetes as type 1 patients rarely are overweight and do not have a sudden loss of body weight with treatment. Prognosis is good, with symptoms remitting over 10-12 months [38].

Rapidly reversible hyperglycemic neuropathy

Recently diagnosed or poorly controlled diabetes mellitus may present with distal sensory symptoms and nerve conduction abnormalities. These symptoms and nerve conduction slowing are reversed promptly with the restoration of glycemic control [39, 40].

Hypoglycaemic neuropathy

It is a distal symmetrical predominantly sensory neuropathy occurring on a background of recurrent episodic symptoms secondary to hypoglycemia [41, 42]. Hypoglycaemia causes effects in both the central and peripheral nervous systems. Energy depletion plays a key role in the pathogenesis of hypoglycemia induced neuropathy [43]. Ischaemia also plays a role [44]. The electrophysiological findings are suggestive of a primary axonal neuropathy with evidence of secondary demyelination. The pathologic changes in hypoglycemic neuropathy may include axonal neuropathy, anterior horn cells destruction in cervical spinal cord with normal dorsal and ventral roots and dorsal root ganglia, or even a normal nerve [45, 46, 47,]. There is a need to exclude the presence of an insulinoma as the literature on humans developing a hypoglycemic neuropathy is small and related to the presence of an insulinoma [48, 49, 50].

Impaired glucose tolerance neuropathy

This occurs in persons with normal fasting glucose and glycosylated hemoglogbin values. However, they have impaired glucose tolerance (IGT) on oral glucose tolerance testing [51, 52]. This form of diabetic neuropathy manifests as a predominantly sensory neuropathy. Small fiber neuropathic changes occur more commonly in persons with IGT than the normal population [53]. This neuropathy is clinically similar to early diabetic neuropathy with a predilection for small fiber damage leading to distressing pain and autonomic symptoms [54]. The nerve fiber loss occurs in a length-dependent pattern [55].

Diabetic autonomic neuropathy

Autonomic nerve involvement is probably the most undiagnosed complication [56, 57]. Diabetic autonomic neuropathy (DAN) may present in multiple organ systems in undiagnosed patients and can result in significant morbidity and mortality [58]. Autonomic dysfunction may already exist at the time of type 2 DM diagnosis, and it's prevalence in the diabetic population rises with time. In type 1 DM, hypoglycemia unawareness is the most common symptom [59]. Autonomic nerve fibers are invariably involved in chronic sensorimotor polyneuropathy, frequently subclinical in the early stages of the polyneuropathy, although it may be detected using sensitive methods to measure and quantify autonomic function. When symptomatic, this may result in impaired sweating and some skin vasomotor changes. However, the autonomic nervous system may become widely involved and dominate the clinical picture. In most patients, the symptoms are not severe, but some have devastating diabetic autonomic neuropathy. The neuropathy may affect all or selected organs or systems innervated by the autonomic nervous system. Thus one or more of the following may develop gastroparesis, diarrhea, constipation, orthostatic hypotension, bladder dysfunction, and erectile dysfunction.

About 40% of diabetic men develop erectile dysfunction which may occur in the absence of, or in association with, other manifestations of diabetic autonomic neuropathy [60]. The clinical examination of the autonomic nervous system is limited. A resting tachycardia and a fixed heart rate of deep breathing or when the patient goes from lying to standing indicate vagal parasympathetic dysfunction. The simple bedside measurement of lying-standing blood pressure change is an important test for sympathetic vasoconstrictor dysfunction. Dry feet connotes a failure of distal sweating. Reduced lacrimation can be detected using Schirmer strips.

Conclusion

It is important for clinicians to be knowledgeable about the various neuropathic complications of DM. Autonomic involvement which is a leading cause of mortality in these patients may mistake for other disease complications. Prompt diagnosis and recognition of these with the institution of appropriate treatment measures would go a long way towards reducing morbidity and mortality outcomes.

Acknowledgment

We thank Dr. Godspower Asekomeh for his advice towards the preparation of this manuscript.

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