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REVIEW

Diabetic Mononeuropathies and Diabetic Amyotrophy

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ABSTRACT

This brief review describes the etiology, pathophysiology, clinical features, therapy and prognosis of the diabetic mononeuropathies and diabetic amyotrophy and neuropathic cachexia. Mononeuropathies include cranial neuropathies, of which the oculomotor nerve is most commonly affected, and are thought to be due to microvascular occlusion. Peripherally, entrapment neuropathies occur in both the upper and lower limbs and are due to compression of an already damaged nerve in anatomically restricted channels. Diabetic radiculopathies occur in the dermatones of the thorax and abdomen, mimicking intraabdominal or intrathoracic pathology. I also describe the features of the rare but very distinctive diabetic amyotrophy and neuropathic cachexia. Overall, the prognosis from these conditions is excellent with residual pain or muscle weakness being rare with the exception of diabetic amyotrophy where the prognosis is dependent upon cooperation with intensive rehabilitation. Therapies include "watchful waiting," physical therapy and rarely surgical intervention, which may be urgently needed for nerve decompression and reversal of motor defects.

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Key Summary Points

The most common diabetic mononeuropathies involve the cranial nerves with the third nerve being the most commonly affected.

Entrapment neuropathies due to diabetes in the upper and lower limbs may need surgical decompression to relieve muscle weakness.

Diabetic radiculopathies occur in the dermatomes of the chest and abdomen, never cross the midline and mimic intraabdominal and intrathoracic pathologies.

Diabetic amyotrophy is due to involvement of the upper and lower lumbar plexi and is a rare condition that presents with severe pain, muscle weakness and atrophy of the muscles of the upper thigh accompanied by severe weight loss.

INTRODUCTION

The term diabetic neuropathy describes a group of syndromes caused by degeneration of the peripheral and autonomic nerves in association with hyperglycemia and/or insulin resistance [1]. Diabetic neuropathy was described long before the discovery of insulin. Painful neuropathy was described in 1883, loss of deep tendon reflexes and nocturnal hyperesthesia in 1884 with cranial mononeuropathy being first described in 1905 [2]. Much later in 1945 diabetic autonomic neuropathy was described [3].

This brief review describes the diabetic mononeuropathies, which, unlike the distal symmetrical and autonomic neuropathies, occur less commonly, are not related to long-term glycemic control and almost invariably resolve usually with minimal, if any, residual damage. Diabetic mononeuropathies include cranial neuropathies, entrapment and pressure neuropathies and radiculopathies. In addition, the syndrome of diabetic amyotrophy and neuropathic cachexia, which is rare and characterized by painful weakness of the thigh muscles accompanied by weight loss, is described.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by the author.

DIABETIC CRANIAL MONONEUROPATHIES

These mononeuropathies involve discrete cranial nerves, usually occur in an older patient and are due to occlusion of the vasa nervorum causing a central infarction of the cranial nerve [4]. Cranial mononeuropathies were first described in 1905 by Dieakufoy who described 58 personal cases in which he described the clinical features of diabetic ophthalmoplegia and later in 1935 by Waite who compared the occurrence of oculomotor palsy in 2002 diabetic patients compared with 4577 non-diabetic subjects and observed a difference in the pupillary response to light [5, 6].

Cranial mononeuropathy is the most common form of diabetic mononeuropathy, and though any cranial nerve may be affected, the nerves, particularly the oculomotor nerve, to the extraocular muscles are the nerves that are most effected.

Third Cranial Nerve (Oculomotor) Mononeuropathy

The onset of ophthalmoplegia is abrupt and in approximately 50% of cases is preceded by several days of unilateral pain above and below the affected eye. On examination there is unilateral external deviation of the affected eye accompanied by ptosis and an inability to move the eye medially and superiorly. A distinguishing feature of a diabetic third nerve palsy, when compared with a non-diabetic third nerve palsy, is that the pupillary response to light is maintained. This is thought to be due to sparing of the peripheral nerve fibers which supply the pupil with only the central area of the nerve being affected by the infarction [7, 8].

With a history of diabetes and the preservation of the pupillary reflex and lack of any other CNS signs or symptoms further investigation may not be necessary, and "watchful waiting" with or without anti-platelet therapy to hasten reopening of the vasa nervorum may be justified [9, 10].

Fourth and Sixth (Trochlear and Abducens) Cranial Mononeuropathies

Next to the third cranial nerve the most commonly involved cranial nerve is the sixth followed by the fourth. In an analysis of 811 cases of oculomotor palsies, diabetes was present in 2.6% of the third nerve palsies, 1.9% of the sixth nerve palsies and 0.6% of fourth nerve palsies [11]. In another series of 24 subjects with diabetes with a cranial mononeuropathy, 17 had a third nerve palsy (2 bilateral), 7 had a sixth nerve palsy, and there were no fourth nerve palsies [12].

These fourth and sixth nerve palsies most often occur in patients above the age of 50, but in this group the prodromal pain is less frequent

and less severe than with a third nerve palsy. Once again, recovery is almost complete within 3 months. Unlike a third nerve palsy, because of the long intracranial courses of the fourth and sixth cranial nerves it is difficult to eliminate an intracranial cause without appropriate investigation and/or neurological consultation. Therefore, watchful waiting is not an option. Within 6–12 weeks resolution, which is almost always complete, occurs.

Seventh (Facial) Cranial Mononeuropathy

There is also an increase in the incidence of Bell's palsy in patients with diabetes. The presentation is the classic ipsilateral facial weakness including the muscles of the forehead, which indicates that this is a lower cranial nerve lesion. In addition, the absence of ageusia (loss of taste) suggests that the infarction of the facial nerve is distal to where the chorda tympani leaves the facial nerve [13].

DIABETIC RADICULOPATHY

Diabetic radiculopathy is a mononeuropathy involving a single nerve root. On occasion multiple nerve roots are involved, and while the condition is self-limited, recurrences in the same or other dermatomes may occur [14].

The patient with diabetic radiculopathy presents with a rapid onset of unilateral and often severe pain in the thorax or abdomen, which is often worse at night [15]. The distribution of the pain is in a single or multiple dermatomes and does not cross the midline.

On examination there is abdominal tenderness that is not lessened by contracting the abdominal wall muscles, which distinguishes abdominal wall tenderness from intraabdominal tenderness because of an intrabdominal etiology where the tenderness will usually decrease with abdominal wall contraction. Similarly, in assessing abdominal wall sensation, hyperparasthesia or occasionally hypoesthesia is detected in the affected dermatome of the chest or abdomen and does not cross the midline. In severe cases, on attaining the upright posture, bulging of the abdominal wall due to denervation and subsequent hypotonia may be observed [16]. Similarly, with chest pain, hyperesthesia or hypoesthesia can be detected in the relevant dermatone and does not cross the midline.

When faced with chest or abdominal pain even when the clinical findings support this diagnosis of a diabetic radiculopathy, investigations to eliminate intrathoracic and intraabdominal pathology and electrophysiological studies to confirm the diagnosis of diabetic radiculopathy should be preformed [17].

Therapy for diabetic radiculopathy is symptomatic with if appropriate the addition of antiplatelet therapy. In severe cases a local anesthetic block can be utilized. The patient should be reassured that the pain will disappear in 6–-12 weeks. However, the patient should also be alerted that another radiculopathy may occur in the same or another dermatome [18].

ENTRAPMENT AND PRESSURE NEUROPATHIES

With diabetes peripheral nerves are more prone to damage from external pressure. In addition, with glycosylation of protein leading to cross-linking of collagen, a less elastic, stiffer and more voluminous form of connective tissue forms, which in anatomically restricted channels exerts pressure on a nerve that may already be damaged because of the presence of diabetes [19, 20].

Carpal Tunnel Syndrome (Median Nerve Mononeuropathy)

The most common entrapment neuropathy is carpal tunnel syndrome where the median nerve is trapped between the transverse ligament below and the carpal bones above [21, 22]. Initially, pain and parathesis involving the medial portion of the palm of the hand, which are aggravated by the utilization of the hand, occur. The symptoms are usually worse at night and may be relieved by "dangling" the hand over the side of the bed [9]. The dominant hand is more commonly affected, and there is a

higher prevalence of carpal tunnel syndrome in females. The prevalence of carpal tunnel syndrome also increases with age and obesity [23, 24].

On physical examination in more advanced cases there is wasting of the thenar eminence, and opponation of the thumb to the little finger is weakened. Sensation is decreased over the palmar distribution of the median nerve (all but the lateral 1½ fingers and the lateral palm). Pressure over the median nerve, usually induced with a patella hammer, worsens the parasthesias (Tinels sign) [25].

When the symptoms of carpal tunnel syndrome interfere with the quality of life or cause hand weakness, surgical intervention to decompress the medial nerve is recommended. Prior to surgery, night splinting and hand physical therapy may be helpful in controlling symptoms. Since the median nerve is also susceptible to compression in the upper forearm by pressure from the pronator teres muscle, localization of nerve compression to the wrist through nerve conductive studies must be preformed to avoid unnecessary and futile surgery [25].

Ulnar Entrapment Neuropathy

The next most commonly affected peripheral nerve damaged from external pressure is the ulnar nerve, which is particularly susceptible to pressure at the elbow in the pisohamate tunnel and presents with paresthesias and numbness of the lateral palm and 1½ fingers. However, of more concern is that severe muscle weakness accompanied by wasting of the interossei may occur with ulnar nerve entrapment since almost all the muscles of the hand, with the exception of the opponens policies and abductor pollicus brevis, are innervated by the ulnar nerve. As a result of this severe muscle wasting there is an imbalance of power between the flexor and extensor muscles of the hand so that the hand may "claw." With severe muscle wasting, surgery to decompress the ulnar nerve is essential and may need to be preformed in an emergency to preserve hand strength. Since the ulnar nerve may also be entrapped at the wrist, nerve conductor studies are essential prior to surgery [26, 27].

Radial Neuropathy

The radial nerve may occasionally be compressed in the axilla (Saturday night palsy) or on the mid-humerus (honeymoon palsy) or at the wrist (handcuff palsy). Pressure on the radial nerve will result in pain and parasthesias in the medial dorsal portion of the hand with minimal motor involvement. Therefore, therapy is usually conservative, and removing pressure from the affected site will usually avoid the need for surgical decompression.

Lower Limb Entrapment Neuropathies

Compression of the lateral cutaneous nerve of the thigh below the inguinal ligament is the most common mononeuropathy in the lower limb. Compression of this nerve causes pain, numbness and parathesis in the antero-lateral thigh (meralgia paresthetica or Bernhardt-Roth syndrome). Surgical therapy is needed occasionally, but should and can be avoided by reducing or eliminating the cause of the pressure [28, 29].

Involvement of the femoral nerve leads to pain, numbness and loss of sensation over the anterior thigh. Motor involvement leads to quadriceps weakness and wasting and unilateral loss of the patellar reflex. Therapy is again symptomatic with aggressive physical therapy to maintain and improve quadriceps strength [30].

Peroneal nerve compression at the head of the fibula not only causes pain, paresthesias and numbness over the dorsum of the foot but can in advanced cases lead to unilateral foot drop, which in turn may cause tripping and falls that may be associated with life-threatening injuries [31]. On occasion the foot drop can be bilateral. Treatment for this "cross leg palsy" is again to remove pressure from the nerve and physical therapy to avoid decompression surgery [32, 33].

Even more rarely compression of the posterior tibia nerve in the tarsal tunnel leads to pain,

parasthesias and numbness of the plantar surface of the foot (tarsal tunnel syndrome) [31].

Very Rare Mononeuropathies

Very rarely mononeuropathies involving the phrenic, long thoracic and obturator nerves may occur in patients with diabetes. The theoretical etiologies are external pressure on the nerve, infarction of the nerve or simply hyperglycemia [18, 34].

Diabetic Amyotrophy and Neuropathic Cachexia

Diabetic amyotrophy and neuropathic cachexia are a lower extremity neuropathy involving the upper and lower lumbar plexi. Other names that are used to describe this syndrome are diabetic lumbosacral radiculopathy, diabetic myelopathy, proximal diabetic neuropathy, Bruns-Garland syndrome and femoral-sciatic neuropathy [35–41].

With diabetic amyotrophy a cutaneous nerve biopsy shows multiple pathologies including ischemic nerve injury, multifocal fiber loss, perineural thickening and degeneration, neovascularization, microfasiculations in addition to swollen axons with accumulated organelles and vasculitis [42].

Nerve conduction studies and EMGs show that although the syndrome is predominantly a motor neuropathy there are sensory and autonomic components [43]. Studies have also suggested that there may be an immuno-mediated inflammatory vasculitis causing ischemic damage. However, immunotherapy to date has not been shown to be efficacious [44]. Cerebrospinal fluid with diabetic amyotrophy is acellular but has raised protein levels, probably due to neuronal damage and/or inflammation [45].

Diabetic amyotrophy is uncommon and usually occurs in men over age 50 who also may have a history of significant alcohol intake and usually have very mild type 2 diabetes, which is often of recent onset. Usually weight loss that can be as much as 40% of initial body weight occurs. Other accompanying symptoms are depression, emotional lability and severe upper leg pain.

On examination, there is severe bilateral muscle weakness and wasting, which is most marked in the pelvic muscle girdle and the anterior thigh muscles. Almost invariably the patella reflexes are absent, and there is objective evidence of distal symmetrical polyneuropathy (loss of sensation and reflexes in the distal lower limb). The muscle weakness results in difficulty and/or an inability to climb stairs or rise from a sitting position [9, 46]. The combination of weight loss with severe neuropathic signs and symptoms in an older patient raises the question of an occult malignancy, which must be ruled out.

Resolution usually occurs in 1–3 years. However, recovery is not always complete and is dependent on compliance with therapy. Generally, symptoms are severe for the first 6 months and gradually decrease following this. Weight loss generally resolves at around 1 year, and muscle strength may improve for up to 3 years [9].

Therapy includes euglycemia, this is usually easily obtained with insulin; this will also increase appetite and facilitate weight gain. Abstinence from alcohol is essential, and a diet high in protein and calories will facilitate weight gain. The most important therapy is physical therapy (the intensity of which is proportional to the degree of recovery) [47, 48]. Rehabilitation can be more effective if the accompanying depression and the neuropathic pain are treated. Only in severe or recalcitrant situations should opiates be utilized for pain control.

CONCLUSION

In this manuscript, I have described the etiology, presentation, diagnostic features, the therapy of and prognosis of the diabetic mononeuropathies, which include cranial nerve mononeuropathies entrapment/pressure mononeuropathies and diabetic radiculopathy. In addition, I have described the features of the rare but very distinctive diabetic amyotrophy

and neuropathic cachexia along with its controversial etiology.

Recognizing these distinctive neuropathies will result in the ability to inform the diabetic patient that the symptoms, though often severe, are self-limited and will usually resolve without resulting in a permanent disability. The patient's concerns of underlying diseases, particularly a cancer, should also be alleviated. Because of this the "informed" patient will be less depressed and stressed. Early diagnosis and therapy should also limit the expense and inconvenience of unnecessary investigation.

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