DIABETIC NEUROPATHY. CLINICAL VARIETIES

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[Neuropatia diabetica. Varietà cliniche]

ABSTRACT

Diabetic neuropathy is a common complication of diabetes, especially in cases of poor control or long duration, which is characterized by its clinical polymorphism whose most common form is distal symmetric polyneuropathy. This paper describes the main clinical varieties.

Key words: diabetes, diabetic neuropathy, polyneuropathy, vegetative dysfunction, mononeuropathy.

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Introduction

Diabetic neuropathy, a common occurrence in neurology, is the most common variety of neuropathy observed in industrialized countries and perhaps even in the world. It is a disease that recognizes inadequate control or long duration of diabetes as risk factors and one of the features that set it apart from many other neurological diseases is its clinical polymorphism whose most common form is distal symmetrical polyneuropathy.

An accurate and especially early diagnosis of diabetes is critical, because the assessment of the prognosis and choice of treatment depend on the degree of metabolic disorder, and this is supported by the fact that in recent years attention has been placed on a possible association between a non-manifest sensory polyneuropathy and impaired glucose tolerance in the absence of overt diabetes, hyperglycemia or increased glycosylated hemoglobin.

It can also be said that diabetic neuropathy is an increasingly spreading pathology correlated with incorrect lifestyles typical of modern society.

The clinical varieties are numerous and the nosography is not clear-cut.

Clinical forms

Currently there is general agreement on the following classification:

Neuropathies:

1) Symmetric:

• Sensorimotor distal symmetric polyneuropathy
• Small fiber neuropathy (Aδ and C fibers)
• Autonomic diabetic neuropathy
• Diabetic neuropathic cachexia

2) Asymmetric:

• Cranial mononeuropathy (3rd, 4th, 6th, 7th, 2nd cranial nerve anterior ischemic optic neuropathy) and occipital neuralgia.

• Somatic mononeuropathy (median, ulnar, or external sciatic popliteal (ESP) nerves)
• Diabetic thoracic radiculopathy
• Cervical and lumbosacral diabetic radiculoplexopathy.

However, for ease of exposition, we will classify them into three main groups:

➢ Distal symmetrical polyneuropathies (PDS) that are equivalent to classical forms of polyneuritis

➢ Autonomic neuropathy

➢ Focal and multifocal neuropathies

Over 80% of patients with diabetic neuropathy fall in the distal symmetric polyneuropathy group[1]. Generally, there is a sensory involvement, because motor deficit is observed only in the most serious forms. We can classify disorders of sensitivity according to the prevalent involvement of large myelinated fibers or of small myelinated and unmyelinated fibers, even though a rigid distinction cannot actually be made since the lesion is often mixed.

When the small fibers are affected, there is a loss of sensitivity of heat and pain, revealed at times by painless burns[2]. The neurological picture is constant: the disorder begins and is prevalent in the extremities of the lower limbs, due to degeneration of the distal portion of the longer fibers. Then the sensory deficit progresses towards the proximal portion of the lower limbs, before reaching the upper limbs where it begins at the tip of the fingers and moves higher and higher into the forearm first and then in the arms.

Therefore, the symptoms are predominant distally and above all symmetrical. In some cases, muscle weakness in the feet and distal part of the legs is an early manifestation and often the patient complains of difficulty in extending fingers and dorsiflexion of the foot. When this symptom progresses, patients report increasing difficulty to walk. In many cases, plantar flexion remains reasonably strong, thus allowing the patients to walk on the front end of their feet.

When sensory symptoms reach to the top of the tibia, numbness or dysesthesia are generally noticed in the fingertips. At this point, the patient may have a considerable instability in their stride due to loss of proprioception and the weakness of the extensor muscles of the legs. When the sensory loss reaches the middle of the thigh and the upper part of the forearm, it can also be seen in the lower abdomen. In severe and more advanced cases, hypoaesthesia and anesthesia may occur in the front part of the trunk due to the degeneration of the terminal part of the fibers that run along the intercostal nerves[3-4].

A triangular area of hypoaesthesia with its apex in the midline of the abdomen is frequently found and may extend to the navel or to the sternum. In this stage of severe neuropathy, patients generally suffer from hyporeflexia or areflexia and are not able to stand or walk independently. The advanced condition polyneuropathy with "glove" or "boot" sensory disturbances (diffuse loss of sensitivity in the distal lower extremities and hands), distal muscle wasting with weakness, and absence of tendon reflexes is an easily recognizable clinical condition. These cases exemplify the concept of a polyneuropathy dependent on the length of the fibers involved since the nerve fibers appear to be involved based on length without regard to the distribution of the roots or nerves of the trunk[5-6].

In the distal polyneuropathy it is easy the detection of complications that include pain and trophic disturbances. Pain is the most common complication, as it affect up to 50.3% of diabetics. The main characteristics of the pain are the nocturnal predominance and association with a certain degree of anesthesia[7]. Sometimes you may also have allodynia and sudden burning. The trophic disturbances basically consist of plantar mal perforans, nervous osteoarthropathies and diabetic pemphigus.

Mal perforans comprises lesions, at times very severe, of the sole of the foot that typically arise in the support or friction points, caused by sensory denervation (in particular nociceptive sensitivity) in patients who can obviously walk. The condition of analgesia and micro-traumas favors fractures, which follow minor traumas of daily life, and more or less torpid osteoarticular infections[8].

The role of the alteration of nociceptive perceptions and the inflammatory response of C fibers (unmyelinated fibers) in diabetic neuropathy with trophic disorders has been emphasized in several physiological studies[9]. The frequency of foot lesions increase depending on the age of the patient and the duration of diabetes. The initial lesion is constituted by a callus, i.e., hyperkeratosis in a support point that causes a zone of serohemorrhagic subcutaneous necrosis that ulcerates if the load or rubbing continues. The foot ulcers are correlated with the involvement of the small fibers[10].

A typical trophic complication of long-standing neuropathies is the involvement of the joints of the tarsus and metatarsus, and, rarely, the ankles[11].

There is a progressive and painless deformation of the foot that in radiological exams results in an increase in bone transparency, the presence of metatarsal fractures, deformity of joint surfaces, and joint disorganization.

Finally, the finding in diabetics of phlyctenular skin lesions, namely intradermal blisters that rapidly grow on feet in a completely painless way in areas affected by sensory neuropathy, gives a picture of diabetic pemphigus[12-13].

Mono- or multifocal neuropathies are typical in adults over the age of 50 years and often reveal long-standing asymptomatic diabetes. In a recent study of 19 patients with a mean age of 66 years, 7 patients had insulin-dependent diabetes known for about twenty years. The external popliteal sciatic nerve was affected in each case, bilaterally in 11 cases, unilaterally in 8 cases; the posterior tibial nerve was involved in 6 cases and the crural nerve in 10 cases. In these patients, severe axonal lesions were detected and a high percentage of the residual fibers were demyelinated. In a third of cases, biopsy showed inflammatory lesions of the nerve with frequent small endoneural hemorrhages[14].

One of the most common forms of focal diabetic neuropathy is diabetic cruralgia or proximal diabetic neuropathy of the lower limbs. Even though it is called cruralgia, the actual localization of the disorders does not always correspond to the branch of this nerve. According to a U.S. study, 14 cases of cruralgia out of 19 are attributable to diabetes. Its clinical expression consists in the sudden onset of intense burning pain, almost like burns, in the front part of the thigh and sometimes in the front inner part of the leg, which occur also at night and cause insomnia and depression. There is also amyotrophy of the quadriceps with a modest deficit of this muscle, which can sometimes be so severe that walking without support is impossible.

Typically, this condition is reversible and the patient improves in a few months, even though there are frequent sequelae such as persistent weakness, amyotrophy, sensory loss and patellar areflexia.

Studies have shown that improvements started after about three months, and pain was the first symptom to disappear, while the motor recovery is almost total[15]. In a recent clinical and morphological study carried out on patients with proximal neuropathy of the lower limbs, in three cases out of ten there was evidence of lymphocytic vasculitis affecting the epi- and perineural arteries of the medial cutaneous branch of the thigh, a branch of the crural nerve. In these cases, it is advisable to administer a corticosteroid therapy for a few weeks, obviously if attempts at compensating diabetes with insulin fail. These results corroborate the role played by ischemia, at times associated with inflammatory phenomena in severe forms of cruralgia and other focal or multifocal neuropathies.

The involvement of the lower limbs also comprises an asymmetric motor deficit characterized by quadricipital amyotrophy that goes by the name of proximal amyotrophic syndrome. This syndrome typically prevents patients from climbing stairs due to proximal weakness and weakness in the anterolateral sections of the leg. There is also a certain muscle tenderness. In rare cases there can also be an isolated lesion of limb nerves and especially of the radial, ulnar and median nerve in the upper limbs, and the sciatic nerve in the lower limbs: in these cases patients needs to be studied as if they were not diabetic to exclude other pathologies.

To get an idea of the rarity of the isolated involvement of limbs, out of a case history of 5000 diabetic patients, it was observed only in 22, namely 0.04%[16]. In these patients, the onset is characterized by painful symptoms, especially if the nerves rich in sensory fibers, such as the median and the ulnar nerve, are affected.

An involvement of the nerves of the truck is also possible and it is manifested through pain (intercostal or thoracoabdominal) with a generally favorable evolution[17] that only rarely is complicated by a major motor deficit of the abdominal wall. In these cases the pain can be burning, stabbing, with belt distribution and usually starts on one side and then becomes bilateral. Cutaneous hypersensitivity and allodynia (usually harmless tactile pain stimuli) may also appear as well as numbness with dermatomal distribution, which is more pronounced in the distal part of the intercostal nerves. Single or multiple spinal roots may be involved. The extent of symptoms may occur in cephalic, caudal or contralateral direction, and pain is thoracic or upper lumbar depending on the involvement of their roots. Very often there is weakness in the area of distribution of the affected nerve roots and at times a swelling of the abdominal wall due to paresis of the abdominal muscles is noticeable.

Thoracic radiculoneuropathy mainly appears in patients older than 50 years of age, more commonly in type-2 diabetes mellitus, and it is often associated with significant weight loss. It is often found in association with distal symmetric polyneuropathy.

The last of the focal disorders to be mentioned here is the involvement of cranial nerves whose incidence in non-insulin-dependent diabetics is equal to 2.2% in men and 3.6% in women. The main events are oculomotor nerve palsies that

almost always occur after 50 years of age. The most frequently affected nerves are the common oculomotor and abducens that are affected with equal frequency. A peculiar feature of the involvement of the third nerve is that inherent motility is very often affected, as seen in 17 out of 22 episodes of oculomotor palsy occurring in a group of 74 patients, 45 of whom had palsy of the 6th pair and 17 with said palsy of the 3rd[18].

The appearance of palsy is often preceded by the onset of pain in the eyeball and periorbital area that was found in 50% of patients. The symptoms include diplopia, which may also be accompanied by ipsilateral headache; forms of stabbing headache[19] and recurring facial palsy secondary to diabetes[20] are also described.

Oculomotor palsy generally has a favorable evolution in a few weeks or months[21].

The involvement of the facial nerve remains very uncommon yet still possible[22].

The third variety to examine is the autonomic neuropathy: the involvement of the autonomic nervous system is one of the features of diabetic neuropathy. The main symptoms result from the involvement of the cardiovascular system, and genitourinary tract but autonomic dysfunction affects many systems and organs. Orthostatic hypotension is very frequent in the mild form, but rare in the more severe and disabling ones: the most common events are fainting, nausea and vomiting, and visual disturbances (blurred vision) while in an upright position. When the pressure drop is too sharp, syncope may even occur because of the failure of the beats to increase due to an alteration in the baroreceptor reflex arc.

The initial phase of cardiac autonomic involvement is represented by tachycardia that typically appears at rest and that consists of the parasympathetic involvement in dysautonomia[23-24]. Then there is a slowing of heartbeat due to the appearance of a sympathetic lesion. Tachycardia, generally, can be seen in the transition from inclined to upright position and is mediated by the parasympathetic system: in diabetic dysautonomia, heartbeat speed increases more gradually compared to the normal condition (maximum frequency at 15th beat). With regard to the disorders of the genitourinary tract, according to many authors, the incidence of cystopathy approaches 80% and in half of cases is associated with impotence. The onset is usually insidious: initially there is a reduction in the sensation of bladder fullness with a decrease in the frequency of voiding. This is associated with a slowing of the urinary stream and such difficult voiding that at times patients need to make an abdominal effort in urination. Since benign prostatic hypertrophy causes similar symptoms, in these cases differential diagnosis is done with this pathology. Impairment of bladder voiding and urinary retention predispose to urinary infections, a condition that, inter alia, is also favored by hyperglycemia. These, in turn, lead to secondary problems of the bladder such as fibrosis and sclerotic and cicatricial outcomes[25].

At the beginning there is an increase in the time interval between urinations, until the patient voids just two or three times a day: as mentioned earlier, it follows that stream force gradually decreases and the subject has the feeling of not having emptied completely the bladder.

Sexual disorders are often associated with prior disorders and affect diabetic males with a prevalence of 40-50%[26]. These often constitute the symptoms of onset. Erectile dysfunction is far more frequent than ejaculation difficulties that generally consist of retrograde ejaculation rather than complete lack of ejaculation.

With regard to the involvement of the gastrointestinal tract, in this case there can be three disorders: constipation, diarrhea and anorectal incontinence[27]. Among these, constipation is perhaps the most common and at times can be severe. Diarrhea can also be very bothersome: it presents with attacks that often occur at night, or after meals, and are watery and at times explosive in nature. Therefore, fecal incontinence can be a feature due to decreased internal anal sphincter pressure as a result of somatic neuropathy[28].

Diarrhea can be chronic, but is often intermittent and may alternate with periods of constipation or normal intestinal function. Diarrhea can be mistaken for anorectal incontinence proper, which is due though, as stated previously, to sphincter anomalies and not to diarrhea itself.

A disorder of the more proximal gastrointestinal tract is also possible[29]. Esophageal motility is often impaired, although it may be equally often asymptomatic or it may cause a feeling of burning and dysphagia and upper esophageal manometry can provide very useful information for diagnosis[30,31].

Gastroparesis is a common manifestation of involvement of the digestive tract in cases of diabetes. It is very often asymptomatic, although, at

times, it can manifest with a feeling of epigastric fullness, more rarely with vomiting of food of a previous undigested meal.

Gastrointestinal dysfunction are primarily due to decreased function of the enteric nervous system that controls many aspects of gastrointestinal physiology, such as, in addition to intestinal motility, disorders in the absorption of water and electrolytes, decreased secretion of intestinal and pancreatic enzymes, abnormal gallbladder function and secretion of bile acids.

Pupillary motility disorders are asymptomatic; in the worst of cases they can cause fogging of vision in the transition from darkness to light. A synthetic study on 36 diabetic patients has shown that patients had an excessively small pupil diameter in dark conditions, and that this diameter varied less than that of a normal person during exposure to intense and prolonged light[32].

There are also other manifestations of diabetic dysautonomia like sweating disorders and sialorrhea. Sweating disorders include episodes of excessive sweating, especially in the upper chest and back[33]. These are linked to the fact that during thermal regulation, patients with severe sensory neuropathy may sweat only in non-denervated regions of the body[33].

The occurrence of hypoglycemic episodes without warning signs may complicate the autonomic neuropathy due to a lack of secretion of catecholamines, usually responsible for vasoconstriction and sweating.

In diabetic dysautonomia, the release of pancreatic glucagon as a response to hypoglycemia, mediated by the vagus nerve, can also be insufficient and lead more rapidly to hypoglycemia[34].

According to reports, the mortality rate in diabetics with autonomic dysfunction after 5 years was 56%.

Another study of survival at 5 years showed that the mortality rate for patients with dysautonomia is 5 times higher than for those without dysautonomia[35]. Postural hypotension, gastroparesis and sudden hypoglycemia contribute greatly to determining a poor prognosis, while diarrhea and impotence are generally not associated with a poor prognosis. One study showed that dysautonomia is an independent cardiovascular risk factor for excessive mortality in type 2 diabetics[36].

Diabetics also appear to have a higher incidence of sudden death than non-diabetics due to dysrhythmias of which diabetic dysautonomia seems to be a concurrent cause.

Finally, it is worth mentioning the high percentage of coexistence, especially in cases of long-standing diabetic disease, of peripheral neurological disorders and central nervous damage, in the form of multi-infarct dementia[37], which may clinically constitute a sort of mixture of damage, which in some cases, though remotely, may recall motor neuron disease[38-39].

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