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Charcot foot and Charcot-Marie-Tooth. An update

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Abstract

INTRODUCTION. Neuropathy or also called peripheral neuropathy is a disease that affects the nerves of the peripheral nervous system. The peripheral nervous system is a network of nerves that connects the central nervous system and the spinal cord. Neuropathy occurs when nerve cells, or neurons, present some alteration which interrupts the interconnection between each one, limiting neuronal electrical activity. Neuropathy can affect one nerve or a combination of nerves. Neuropathy is very common. It is estimated that about 25 to 30% of Americans will have neuropathy. Neuropathy occurs in 60 to 70% of the population suffering from DM2.

MATERIAL AND METHOD. An internet search was carried out in the Pubmed and Scielo databases and national journals related to the subject with the keywords type 1 and type 2 diabetes mellitus, Charcot foot and Charcot-Marie-Tooth, selecting 31 current references on both topics.

DISCUSSION. Charcot neuropathy is a disabling complication of DM. Its diagnosis implies a physical examination, anamnesis, supported by radiological studies that allow differentiating this complication from other disorders that affect the distal limbs in the same way, such as osteomyelitis. Initially, its opportune diagnosis allows establishing primary treatments with the purpose of avoiding the fearsome complications of the disease, leaving another type of treatment as a last option.

CONCLUSION. There are multiple diseases that affect the peripheral nervous system, but the two main ones are Charcot Foot and Charcot-Marie-Tooth disease.

Keywords: Diabetes mellitus, Neuropathy, Charcot foot, Charcot-Marie-Tooth disease.

INTRODUCTION

In 1886, Jean Martin Charcot and Pierre Marie, in France, and independently Howard Henry Tooth, in England, made the first descriptions of the disease, calling it peroneal muscular atrophy, a pathology that would later be named Charcot-Marie-Tooth disease (CMT1), which is a hereditary sensory-motor neuropathy (NHSM).

CMT1 is characterized by degeneration or abnormal development of peripheral nerves. In most cases it appears in childhood and is characterized by a clumsy gait due to predominantly distal muscle atrophy in the extremities and foot deformity in the form of foot drop.

The prevalence of CMT1 disease ranges from 10 to 30 cases per 100,000 inhabitants, characterized by degeneration or abnormal development of peripheral nerves. It currently affects about 1 in 2,500 people. It can start during adolescence or later in life (1).

At present, more than a dozen variants of this disease are known, which vary according to the mechanism of inheritance and are autosomal dominant, autosomal recessive or dominant linked to the X chromosome. It is transmitted in an autosomal dominant (AD) manner in most cases, but also in an autosomal recessive (RA) and X-linked form. It presents an estimated incidence of 1 per 2,500 live births and a prevalence of 17 to 25 per 100,000 inhabitants, which is why it is considered the most common hereditary neuromuscular disorder (2).

On the other hand, Charcot foot due to diabetes mellitus (DM) is another progressive degenerative arthropathy associated with various types of neuropathic diseases, although it occurs more frequently in neuropathy produced by DM2.

This arthropathy affects the foot and produces structural deformities with the possibility of developing ulcers and osteomyelitis.

After in 1868 Jean-Marie Charcot made the first detailed description of the rapid evolution, deterioration and instability of the joints in patients with tabes dorsalis (neurosyphilis). In 1892 Sokoloff revealed the association of neuropathic joints of the upper extremity with syringomyelia. In 1936 Jordan associated DM2 with neuropathic changes in the foot and ankle (3).

Diabetes, syphilis, and syringomyelia are the clinical entities most commonly associated with neuropathic arthropathy. Leprosy, spina bifida, congenital insensitivity to pain, and many other disorders are associated with this condition, but less frequently. More than 24 diseases have been reported to date as causing "Charcot's joint". Today DM2 is the main aetiology.

Charcot neuroarthropathy is a progressive degenerative disease that affects the joints of the foot. It was first observed in leprosy patients and alcoholics. Any condition that causes sensory or autonomic neuropathy can lead to Charcot deformity (3). Objective, Determine the specific cause of each disease in order to differentiate them.

MATERIAL AND METHODS.

Literature review by collecting data and updated in-

formation. An internet search was carried out in the Pubmed and Scielo databases and related national and international journals on the subject with the keywords type 1 and type 2 diabetes mellitus, Charcot foot and Charcot-Marie-Tooth, selecting 31 references.

DISCUSSION

Neuropathy

Neuropathy or also called peripheral neuropathy is a disease that affects the nerves of the peripheral nervous system. The peripheral nervous system is a network of nerves that connects the central nervous system and the spinal cord.

Neuropathy occurs when nerve cells, or neurons, present some alteration which interrupts the interconnection between each one, limiting neuronal electrical activity. Neuropathy can affect one nerve or a combination of nerves. Neuropathy is very common. It is estimated that about 25 to 30% of Americans will have neuropathy. Neuropathy occurs in 60 to 70% of the population suffering from DM2 (4).

The International Society for the Study of Pain (IASP) defines neuropathic pain as: "pain initiated or caused by a primary lesion or dysfunction of the central or peripheral nervous system with a high degree of complexity, frequently defined as presenting in the absence of tissue damage. Concurrent or progressive acute; its intensity can vary from mild to severe and disabling, which can even lead the sufferer to suicidal tendencies. It is characterized by being dysesthetic, burning, burning, paroxysmal, with sensory deficit and abnormal response to stimuli (allodynia and hyperpathy)".

It is important to assess the feet at each consultation in order to stratify them and proceed with the corresponding treatment. Causes of neuropathy. Causes can be acquired or hereditary

Charcot-Marie-Tooth (CMT) disease, also called peroneal muscular atrophy, is an inherited neuropathy characterized by degeneration or abnormal development of peripheral nerves. In most cases it appears in childhood and is characterized by a clumsy gait due to predominantly distal muscle atrophy in the extremities, as well as foot drop-shaped foot deformity.

At present there are variants of this disease that appear according to the inheritance mechanism as autosomal dominant or recessive, or linked to the X chromosome; in its electrophysiological manifestations (demyelinating or axonal), depending on the causal mutant gene.

The most common hereditary neuropathy is CMT disease, which affects both motor and sensory nerves. It affects about 1 in 2,500 people in the United States. These cause weakness in the foot and lower leg muscles. Foot deformities that make walking difficult and often result in falls are also common (5).

The effect of sustained hyperglycemia and increased proinflammatory mediators that can activate osteoclasts through the RANKL (Receptor Activator for Nuclear Factor κ B Ligand) pathway, which is a receptor that stimulates the fusion of preosteoclasts, promotes the adherence of osteoclasts to bone, acti-

vates its function and increases its survival by preventing apoptosis.

In the same way, they can be activated by independent pathways to this ligand, as well as the dysfunction of the counterregulatory mechanisms of osteoclastic activity in the acute phase of the disease. CMT disease is the most common hereditary neuropathy. Classically divided according to its pattern of inheritance and median nerve motor conduction velocity (MCV) abnormality, CMT includes five broad categories: CMT1 (autosomal dominant [AD] or sex-linked inheritance, and MCV < 38 m/s) ; CMT2 (AD or sex-linked inheritance and MCV > 38 m/s); CMT4 (autosomal recessive [AR] inheritance and very slow MCV); AR-CMT2 (recessive form with VCM > 38 m/s), and DI-CMT (intermediate form with AD inheritance and VCM between 30 and 40 m/s).

Despite its stereotyped clinical picture (basically, sensory-motor polyneuropathic semiology and pie cavus), CMT has turned out to be one of the syndromes genetically complex neurodegenerative disorders, with 31 cloned pathogenic genes (6).

Anatomically and functionally, the peripheral nerve is of a complex structure, as it connects the spinal cord with sensory receptors and distal muscles. Most of the peripheral nerves incorporate into their structure both sensory and motor fibers, as well as vegetative fibers, making evident the complex function of these nerves. Microscopically, the normal structure of the axon in peripheral nerves includes myelinated segments and unmyelinated segments; the latter are called Ranvier nodes.

The primitive or immature Schwann cell has the ability to migrate from the neural crest and make contact with developing peripheral axons; it then covers groups of immature axons and initiates intercellular signaling processes. When the Schwann cell unites with its axon, the expression and regulation of genes that code for most of the proteins that form myelin originate, so the cell is established as myelin; when this attachment is not achieved, the immature Schwann cell remains an unmyelinated cell.

The myelination process is dynamic, since it depends on the constant cell-axon interaction; when this interaction fails (peripheral nerve sectioned), a process of demyelination begins in the axon (2, 7).

Charcot neuropathy in diabetic foot DM2 is defined as the set of metabolic syndromes characterized by sustained hyperglycemia, due to an absolute or relative deficit in insulin secretion, together with different degrees of peripheral resistance to its action.

The number of people with DM2 went from 108 million in 1980 to 422 million in 2014. The prevalence has been increasing rapidly in low-income countries low and middle income than high income. T2DM is a major cause of blindness, kidney failure, myocardial infarction, stroke, and lower limb amputation (8, 9).

According to the American Diabetes Association, more than 25 million people in the United States have this disease, about 8% of the population also suffers from it and is undiagnosed. From 60 to 70% of people with diabetes develop peripheral nerve

damage, and up to 29% of these patients may have Charcot arthropathy. Charcot's neuroarthropathy has a prevalence of 1 in 680 diabetic patients (10).

Etiopathopathogenesis of diabetes

The main mechanisms involved in the etiopathogenesis of Diabetes Mellitus are: genetic predisposition, immunological phenomena, environmental factors and metabolic alterations. The importance and specific weight of each of these factors will depend on whether it is DM 1 or DM 2.

DM1 is the result of an autoimmune reaction mediated by T lymphocytes and determined by genetic and/or environmental factors, which produces a selective destruction of pancreatic beta cells. A large number of genes have been implicated, establishing a balance between predisposing and protective alleles. The influence of both one and the other in the development of DM1 depends on factors such as race, degree of HLA (human leukocyte antigen) identity, and geographic distribution of alleles, among others. Genetic susceptibility is well recognized in the development of DM2, such that the prevalence in individuals with a first-degree family history is higher than expected.

The development of the diabetic foot comprises a neuropathic, vascular and infectious (immunopathy) multifactorial etiological triad, which, due to the intervention of external or internal trauma, develop a foot lesion. The main cause of ulcers is diabetic polyneuropathy, due to the risk posed by loss of sensitivity, compared to the slightest trauma. In addition, there are other etiological factors that increase the risk of foot ulcers, such as structural deformities, limited joint mobility, and peripheral vascular disease.

Diabetic foot lesions can be neuropathic (55%), ischemic (10%) or neuroischemic (35%) depending on the etiological factor involved in their development. Most of the complications that occur in DM2 arise from poor control and management by the patient. One of the most critical foot problems that can cause these complications is Charcot arthropathy, which in advanced cases leads to limb amputation.

Diabetic foot ulcers are a very common complication, which in turn have two or more risk factors, where diabetic peripheral neuropathy and peripheral arterial disease play a fundamental role. Neuropathy causes numbness and sometimes deformity of the foot as it progresses, often causing maldistribution of load on the foot. People who suffer from neuropathy and suffer minor traumas regarding inadequate footwear or external injuries, can lead to foot ulceration. Loss of protective sensation, foot deformities, and limited joint mobility can result in abnormal biomechanical loading on the foot (11).

Directly affecting its biomechanical functioning, resulting in thickening of the skin in the form of a callus. This callus conditions a greater increase in foot load, frequently with subcutaneous hemorrhage and eventually ulceration of the skin. Whatever the primary cause of the ulceration, it means that continuing to walk on the insensitive foot impairs the healing of the ulcer (12).

However, most foot ulcers are purely neuropathic or

neuroischemic, the latter being caused by a combination of neuropathy and ischemia. In patients with neuroischemic ulcers, despite having severe foot ischemia, symptoms may be absent due to the presence of neuropathy (13, 14).

Type 1 and type 2 DM are characterized by a lack of insulin that is produced by the pancreas, which leads to a state of hyperglycemia that can progress to diabetic ketoacidosis, which if not treated immediately can lead to death or its failure. defect lead to chronic complications. Two of the diseases that appear in this type of patients are Charcot foot and CMT disease that causes neuromuscular disorders affecting the peripheral nerves and the peripheral vascular system causing deformation of the foot or feet that will require specialized treatments for their conservation or termination. in their amputation (15).

Charcot neuropathy is a disabling complication of DM. Its diagnosis implies a physical examination, anamnesis, supported by radiological studies that allow differentiating this complication from other disorders that affect the distal limbs in the same way, such as osteomyelitis alone or as part of the syndrome. Initially, its timely diagnosis allows establishing primary treatments with the purpose of avoiding the fearsome complications of the disease, leaving another type of treatment as a last option (16).

The nerve defect that causes pain, numbness, tingling, edema and muscle weakness in different parts of the body, in this case in the extremities, can be defined as peripheral neuropathy. This complication is produced by different causes, among them; hereditary or acquired neuropathy. Therefore, its progression and non-pertinent intervention generates complications or functional disability for the patient.

Charcot neuropathy in diabetic foot

By its two general classifications, in the acquired type neuropathy is the Charcot foot neuropathy due to DM.

Charcot neuroarthropathy or Charcot disease (CAP) is a rare but serious and debilitating complication of DM and can lead to amputations and increased mortality due to its progression. This entity is characterized by a destructive inflammatory process of the foot and ankle of a progressive course and with a non-infectious nature, which with its complication generates bone, joint and ligament damage that in turn compromises the structure and function of the foot, presenting with microfractures, fractures and dislocations of the foot bones and in severe cases amputation.

Occasionally a patient with Charcot arthropathy due to DM is mostly pain free, but may have other symptoms. The most noticeable sign of an early Charcot foot is swelling of the foot. This can occur without prior injury; foot redness can also occur in the early stages as well as swelling, redness and changes in bone structure; Without appropriate control treatment, it can evolve into a fracture or amputation of the limb.

CAP is a destructive systemic disease that generates pathological changes in the musculoskeletal system, causing fractures, dislocations and deformities with

risk of ulceration and infection, which compromise the foot and ankle.

The morbidity attributable to the diabetic foot can be divided into three categories: a) abscess and osteomyelitis, b) neuro-arthropathic deformity, and c) ischemic disease and gangrene.

One of the most common causes of hospitalization for diabetics is a foot ulcer or infection. Once a foot ulcer or infection occurs, the risk of lower limb amputation increases by 8, and within two years of said amputation 36% of patients will have died (18).

A problem to consider is the evaluation of the destination that the contralateral limb will have because it will be subject to greater pressures due to the impediment of the diseased foot to support the weight of the body. Félix, et al, in a study found that 20% of patients with diabetic foot developed ulcers on the opposite limb, that is, almost half of patients with diabetic foot, which leads to greater morbidity and mortality (19).

Secondary treatment consists of fixation or artodesis of the ankle and foot in order to avoid ulcerations, deformities, instability and finally amputations. Griffits et al, in their study found that it is necessary to educate patients, meet their expectations and improve adherence to treatment (20).

Regarding imaging support studies, Magnetic Resonance Imaging (MRI) is useful for establishing an early and accurate diagnosis for the treatment of these patients. When patients are in stage 0 and immobilization was performed during the first month of symptoms, approximately 70% of patients were deformity-free for an average of 4 months of immobilization, however, when patients were classified as stage 1, about 2 months after the start of the Symptoms, an immobilization time of 5 months was necessary with only 30% recovery, so this study is important to stage the progression of the disease (Table 4) (21).

Keukenkamp R et al. (22) carried out an investigation in patients with deformed Charcot foot regarding plantar pressure, shoe adherence and plantar ulcer recurrence, finding effective offloading with adherence in these patients, but although this adherence protects against plantar ulcer recurrence, a large proportion of patients still experience recurrence of these ulcers, therefore improvements are recommended

in adherence and in the design of personalized footwear to improve these results. The main characteristics of Charcot's foot in 40 patients studied by Thewjitcharoen Y, et al (23) found 13 acute cases and 27 chronic cases with DM2, highlighting that this diagnosis is not very accurate as it is confused with cellulitis in almost a third of the patients, osteomyelitis in 15% concluding that this disease occurs in poorly controlled diabetics with inadequate treatment and poor results that affected the number of amputations.

On the other hand, one of the neuropathies described is CMT hereditary neuropathy, a pathology capable of affecting motor and sensory nerves.

Classically, CMT is divided into (CMT1) when the disease is primarily demyelinating with motor nerve conduction velocity < 38 m/s, and type 2 (CMT2) when the disease is axonal with nerve conduction velocity > 38 m/s. There is also an intermediate presentation where the nerve conduction velocity is between 25 and 45 m/s. Another subclassification is based on a hereditary pattern which can be autosomal dominant, or autosomal recessive linked to X (24).

CMT1 is a sensory motor neuropathy with slow and progressive progression frequently associated with cavo-varus foot deformity and for its assessment there are scales used for its classification and management. Rambelli C et al (25) reviewed them to assess deviations from the NCMT and found that the six-item scale (FPI-6) demonstrated high applicability in different cohorts after brief training of physicians, as well as having psychometric properties.

FPI-6 consists of six items (26)
1. Palpation of the head of the talus; 2. Supra and inframalleolar peroneal curvature; 3. Position of the calcaneus in the frontal plane; 4. Prominence of the talo-navicular region; 5. Congruence of the internal longitudinal arch (ALI); 6. Abduction/Adduction of the forefoot with respect to the hindfoot.

In CMT1, the affected person loses the ability to feel vibration, pain, and temperature. The weakness starts in the lower legs. It causes the inability to flex the ankle and therefore raise the front of the foot, causing foot drop and in turn atrophy of the calf muscles (stork leg). According to its progression, there is involvement of the upper limbs in which the hands and feet, as a whole, do not perceive position, vibrations, pain or temperature. This loss of sensitivity ascends progressively.

Genetic diagnostic strategies for CMT must be addressed through interaction between clinicians and geneticists and once the diagnosis has been established through clinical examination and findings, electrophysiological, the search for genetic evidence is the next step. Clues to genetic origin are relatively easy to find in family histories by asking affected patients specifically about all in the infant stage. Acquired neuropathies should be distinguished from genetic neuropathies by history, MRI, and cerebrospinal fluid protein levels. Patients should be referred for molecular diagnosis only when there is suspicion of hereditary neuropathy. Genetic tests should not be offered to eliminate the possibility of hereditary neuropathy since the causative gene and mutations cannot identify more than 40% of hereditary cases due to their heterogenic nature, additionally they can be unnecessary work and high financial costs. (27).

A large proportion of mutant proteins in the axonal CMT have documented roles in mitochondrial motility, suggesting that organelle trafficking may be a common mechanism underlying this disease (28). The discovery of various genetic mechanisms during the last 30 years have laid the foundations for a wide range of therapies for, up to now, a group of incurable demyelinating diseases. Many therapeutic approaches including gene silencing and replacement therapies as well as small molecule therapy are preclinical trials that have reached clinical

trial stages (29).

At present there is still no treatment available for CMT neuropathy, the usual is rehabilitation, surgery for bone deformities, and symptomatic treatment of pain, fatigue and cramps that accompany CMT. Various attempts include gene silencing, to stop the overexpression of the PMP22 (Peripheral Myelin Protein 22) gene in the CMT1A type. PXT3003 (Treatment based on the combination of baclofen, naltrexone, and D-sorbitol) is the most advanced compound tested against CMT1A which is in phase II of experimentation. Gene therapy for the replacement of defective genes tested in experimental animals, Modulation of Neuroregulin that determines the thickening of myelin is promising. Other potentially useful therapies target macrophages, lipid metabolism, and the Nav 1.8 sodium channel (Vertex, multiple pain indications) in demyelinating CMT and the P2X7 receptor (P2X Purinergic Receptor 7 protein-coding gene) that regulates the Calcium flux into Schwann cells in CMT1A. Other attempts are directed towards the correction of metabolic normalities that include sorbitol accumulation through bi-allelic mutations of the sorbitol dehydrogenase gene (SORD) and neurotoxic glycosphingolipid mutations in HSN1 (Hereditary neuropathic sensor type 1) (30).

Genetic modifications in rare diseases such as CMT1A have shown considerable variation in disease expression. CMT1A is caused in most of these patients by a uniform duplication weighing 1.5 Mb involving the PMP22 gene. In such a way that SIPA1L2 is a potential genetic modifier of the phenotypic expression of CMT1A that offers a new route of therapeutic intervention (31).

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