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Case Report

Unveiling Hereditary Neuropathy with Liability to Pressure Palsies: A Case Report of Positive Genetic Test Without Familial History

Diagnóstico de Neuropatia hereditária com paralisia sensível à pressão na ausência de história familiar: Relato de caso

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ABSTRACT: Hereditary Neuropathy with Liability to Pressure Palsies (HPNN) is an autosomal dominant condition that most commonly with an acute onset, sensory motor, focus and unpainful mononeuropathy. Approximately 80% of patients have a 1.5 Mb deletion on chromosome 17p11.2, enveloping the peripheral protein of myelin 22 (PMP22) gene. Only a small part of patients' disease is induced by de novo mutations in the PMP22 gene. In this case report, we describe an adult patient, with no family history, complaints of recurrent mononeuropathies in the upper limbs for 1 year with an initial diagnosis of tendosynovitis. After investigation with an electroneuromyography study and ultrasonography, diagnosis of HNPP by genetic test was confirmed. Patient then guided to behavioal measures and rehabilitation. HNPP until now have no curative treatment, with symptoms relief the main therapeutic.

KEYWORDS: Hereditary Neuropathy; Liability to Pressure Palsies; HNPP.

RESUMO: A Neuropatia hereditária com paralisia sensível à pressão (HNPP) é uma condição autossômica dominante que se apresenta mais comumente com uma mononeuropatia de início agudo, sensitivo-motora, focal e não dolorosa. Aproximadamente 80% dos pacientes possuem uma deleção de 1,5 Mb no cromossomo 17p11.2, envolvendo o gene da proteína periférica da mielina 22 (PMP22). Em apenas uma pequena proporção de pacientes a doença é causada por mutações *de novo* no gene PMP22. Relatamos o caso de um paciente adulto, sem história familiar, apresentando por 1 ano sintomas de mononeuropatias recorrentes em membros superiores com diagnóstico inicial de tendossinovite. Após investigação com estudo eletroneuromiográfico e ultrassonografia, diagnóstico de HNPP confirmado por teste genético. Paciente então orientado a medidas comportamentais e reabilitação. A HNPP até o momento não possui tratamento curativo, sendo o alívio dos sintomas a principal terapia aplicada.

PALAVRAS-CHAVES: Neuropatia hereditária; Paralisia por pressão; HNPP.

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INTRODUCTION

Hereditary Neuropathy with Pressure Palsies (HNPP) is a rare, demyelinating sensory-motor disorder characterized by focal and recurrent paresthesias (numbness, pricking, tingling sensations) and limb weakness, also focal1. It mainly occurs in areas where chronic compression can occur, such as ankles, wrists, back of the knees or elbows. These symptoms can be triggered by low-intensity physical activities, minor injuries and local compressions. The diagnostic suspicion of HNPP arises upon the manifestation of painless monoparesis and paresthesias that occur acutely and recurrently subsequent to compression of the affected region. Improvement in the condition is observed upon cessation of force in the area. The symptoms tend, in most cases, to start in adolescence or early adulthood, but can appear in other age groups3. HNPP is a genetic condition in which approximately 80% of cases occur by hereditary transmission with an autosomal dominant pattern2, thus, de novo mutation causes occur in a minority of patients. Regarding sex-related epidemiology, it equally affects both men and women2. Most patients commonly report the onset of the first episode in the second or third decade of life, but some individuals with HNPP may present the condition at older ages. The disease's low prevalence, and consequently, the lack of familiarity with its symptoms, can lead to incorrect diagnoses or underdiagnoses. Due its clinical characteristics, such as painless muscle weakness, paresthesias, hypoesthesia, and hyporeflexia, are common to other disorders of the peripheral nervous system, HNPP poses a significant diagnostic challenge. It is necessary to distinguish it from more common conditions such as radiculopathies and Guillain-Barré Syndrome, as well as from other rare genetic diseases such as Charcot Marie Tooth Disease 1;4. The diagnosis is established through the identification, via molecular genetic testing, of either the recurrent 1.5 Mb deletion on chromosome 17p11.2, a novel deletion encompassing PMP22, or a variant within the PMP22 sequence5. However, it is the careful clinical evaluation and suggestive electroneuromyographic examination that incite suspicion for the genetic test request.

OBJECTIVES

The aim of this case report is to analyze and describe the clinical presentation of an adult who tested positive for hereditary neuropathy with liability to pressure palsies (HNPP), with the intention of stimulating discussion surrounding this rare condition and emphasizing the importance of considering its diagnosis even in the absence of familial precedent. Furthermore, this report underscores the significance of careful evaluation of potential differential diagnoses within similar clinical contexts.

CASE REPORT

A 44-year-old man, without any previous family medical history, presented with an acute sensory-motor deficit in the territory of the ulnar nerve of the left upper limb subsequent to falling asleep on the limb. He reported no significant trauma or pain. He was diagnosed with tenosynovitis in the emergency room. Since then, he has reported new episodes of tingling and loss of strength in the upper limbs after simple activities such as carrying a shopping bag. He was advised to use only non-steroidal anti-inflammatory drugs, without showing clinical improvement. As a result of the heightened recurrence of symptoms and the lack of improvement, he sought his initial consultation with a neurologist one year following the onset of symptoms. His physical examination was largely unremarkable. He demonstrated negative Tinel and Phalen tests, yet exhibited slight hyporeflexia in the upper limbs, particularly pronounced on the left side. Laboratory tests revealed normal levels of blood sugar, kidney function, and thyroid hormones. There were no indications of hypovitaminosis from a nutritional standpoint. Serological tests, including screening for leprosy, returned negative. The electroneuromyographic examination revealed focal demyelinating involvement with secondary axonal degeneration in the median nerves at the wrist level, in the ulnar nerves along the elbow segments, and in the left ulnar nerve at the wrist region (Guyon's canal). Subsequently, the ultrasonographic examination of the wrist revealed a thickness measuring 9 mm2, confirming an increase in nerve thickness at a compression site within the wrist. Given the clinical presentation and suggestive findings, a genetic test was requested, which identified a heterozygous deletion approximately 1.37 Mb in size within the PMP22 gene, indicative of compatibility with HNPP diagnosis. The pathophysiological mechanism underlying the development of an HNPP phenotype involves the underexpression of the PMP22 gene, either due to gene deletion or mutation-induced gene inactivation. Following this diagnosis, the patient underwent genetic counseling, was referred to occupational therapy, and received guidance regarding risk factors.

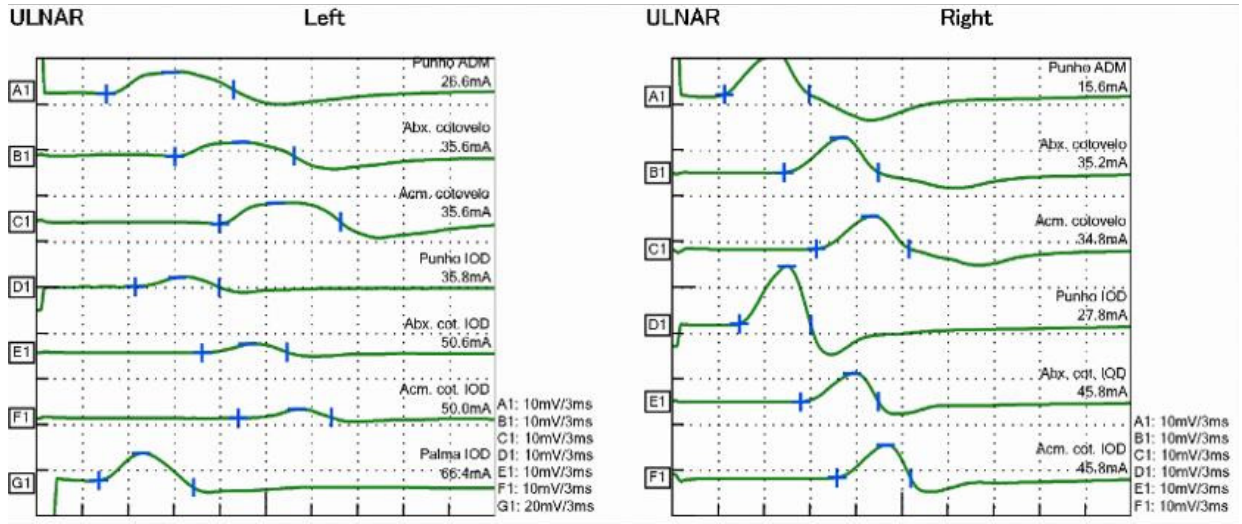

Figure 1 - The study of motor conduction shows changes such as prolonged distal latencies of compound muscle action potentials of the left ulnar nerve and reduced conduction velocities of the ulnar nerves along the segments through the elbows.

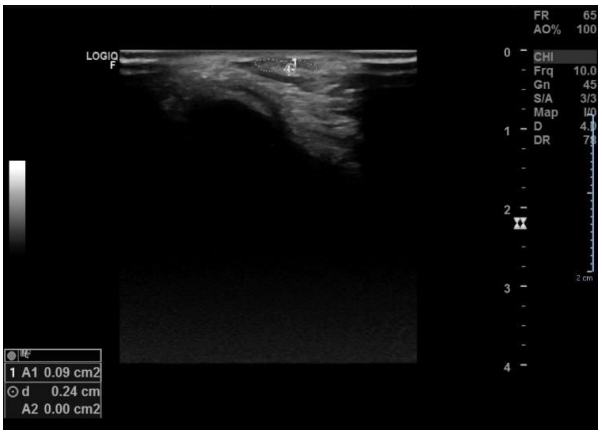

Figure 2 - View of the median nerve compression area at the wrist. The cross-sectional area revealed a widening of 9 mm2 of the median nerve in the wrist region, with the normal reference value ranging from 5.5 to 5.7 mm2.

DISCUSSION

HNPP is a rare and challenging condition where diagnostic suspicion is based on a combination of characteristic clinical symptoms, family history consistent with autosomal dominant inheritance and electrophysiological tests. The rarity of such conditions often extends the diagnostic process for patients. The presence of nonspecific symptoms, shared with other neuropathies, often leads individuals with HNPP to initially receive misdiagnoses, such as carpal tunnel syndrome, radiculopathies, or orthopedic conditions, as evidenced in the reported case. The electroneuromyographic examination is of utmost importance for the diagnosis of HNPP. Nerve conductions reveal a decrease in nerve conduction speed, most often in areas of compression. Also, as already mentioned, the genetic test is confirmatory of the pathology when it presents with deletion of the PMP22 gene. This same gene, during meiosis, can manifest a duplication, resulting in a different condition known as Charcot-Marie-Tooth Disease (CMT). This syndrome, although it involves the same gene as HNPP, has a distinct clinic. In CMT, motor and sensory symptoms are slowly progressive, and can also present with areflexia, hair loss, bone deformity, and distal muscle atrophy. Ultrasonography can also be used as a diagnostic tool for HNPP. The primary ultrasonographic observation is the potential thickening of multiple nerves at characteristic compression sites. However, certain patients exhibiting clinical and electrophysiological indications of HNPP may present normal ultrasound results. In the differential diagnosis of multiple mononeuropathies with focal conduction slowing, it should be considered to investigate vasculitic neuropathies (mononeuritis multiplex) and leprosy. Mononeuritis multiplex also manifests as an asymmetric sensory-motor peripheral neuropathy; however, it typically presents with notable pain. Moreover, associated with the peripheral neuropathy presentation, we may observe systemic symptoms indicative of underlying conditions such as Systemic Lupus Erythematosus, Rheumatoid Arthritis, or Polyarteritis nodosa. In leprosy neuropathy, there is frequent involvement of autonomic fibers, in addition to sensory and motor fibers. Thus, autonomic manifestations such as loss of sweating are commonly found. On physical examination we can find hypersensitivity to palpation and thickening of the nerves. In addition, in case of mononeuropathies, we should rule out other acquired causes beyond infectious and vasculitic/rheumatologic ones, such as: diabetes;

excessive use of alcohol; kidney disease; deficiencies of B12 vitamin, copper, and folic acid. So far, there is no definitive cure for HNPP. Treatment primarily focuses on preventing compression-related damage, with an emphasis on alleviating symptoms. Understanding the patient's living conditions is crucial to identifying modifiable factors and consequently enhancing their quality of life. Bjelica et al. (2020) conducted a study indicating that the diminished quality of life among patients with HNPP correlates with factors such as low education level, occupation type, a high number of affected nerves, severe pain, depression, and fatigue. Therefore, treatment is based on rehabilitation and change of habits, aiming to avoid new compressions in places like the wrist, elbow, and popliteal fossa. For highly symptomatic patients, therapy is done with common drugs for neuropathic pain, such as gabapentin, pregabalin, and tricyclic antidepressants. It is imperative to prioritize the psychological well-being of these patients, as depression scores among individuals with HNPP mirror those observed in patients with CMT. This similarity arises from factors such as acute relapses, lifestyle modifications, and, most significantly, the apprehension of disease recurrence.

CONCLUSION

Despite the diagnostic complexity, as in the presented case, some information from the history and physical examination assist in the diagnosis. These include the recurring nature of symptoms and their temporal association with trauma, traction, or nerve compression. While a family history of HNPP often proves valuable in clinical assessment, it is not a prerequisite for establishing the diagnosis. In our case, suspicion arose from the typical characteristics of HNPP and the electroneuromyographic findings that evidenced an increase in nerve conduction latency, reduction in conduction speed, and conduction block at compression points. For clarification of the suggestive picture and after exclusion of metabolic and infectious causes, a genetic test was requested that confirmed a less common form of the disease's emergence through a new mutation in the PM22 gene. In summary, the case we discussed underscores how knowing the signs of a condition helps with diagnosing it, especially when dealing with HNPP. Tests like electroneuromyography and genetic testing play vital roles in diagnosing this condition. Without adequate awareness of the disease, there's a risk of misdiagnosis. Therefore, it's crucial to consider various possibilities, especially when the neurophysiological findings and family history are unusual. While there's no cure, early diagnosis, genetic counseling, rehabilitation, and advice on managing risks can reduce the impact of the disease and enhance the patient's quality of life.

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