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Case Report

When arthralgia is not arthritis

Juan Politei[1], Graciela Remondino[2], Ricardo Heguilen[3], Eric Wallace[4], Consuelo Durand[1], Andrea Schenone[1]

Abstract

The presence of distal extremity pain in children and adolescents usually triggers the search of rheumatologic diseases without considering non-rheumatologic causes of joint pain. Approaching distal extremity pain with a complete differential diagnosis, including non-rheumatologic entities, may hasten diagnosis, thus decreasing cost and aiding in earlier initiation of appropriate therapy. To present a case of a patient who after years of work up of arthralgia, which was actually attributed to rheumatologic causes, had an inherited metabolic disease. A 32-year-old male presented to the clinic with complaints of distal pain in his four limbs, predominantly in the hands, since he was 8 years. After 6 years of consultation in various pediatric centers, he was diagnosed with growing pains. At the age of 15 years, laboratory investigations began targeting rheumatologic causes of his symptomatology, and after 9 years, the diagnosis of chronic kidney disease of unknown etiology was made. Because of the constellation of signs and symptoms and his family history, an analysis of α-galactosidase A enzyme activity was conducted and Fabry disease was confirmed. Rheumatologists and immunologists may be the first encounter patients with Fabry disease. Thus, if Fabry disease is not considered at the differential diagnosis, an opportunity is missed for early initiation of a therapy.

Keywords: Arthralgia, Fabry disease, distal extremity pain

Introduction

The presence of distal extremity pain in children and adolescents usually triggers the search for rheumatologic diseases without thought to non-rheumatologic causes of joint pain. Even when classic signs of articular inflammation (swelling, reddening, local temperature increase, pain, etc.) are absent, laboratory evaluations, including non-specific serological markers of inflammation (C-reactive protein, erythrocyte sedimentation, etc.), and autoantibodies are ordered. In the absence of serological evidence of a disease, several rheumatic diseases cannot be completely excluded. As such, in many cases, it is necessary to perform tissue biopsy (e.g., nerve biopsy in peripheral nervous system primary vasculitis) to definitively confirm or exclude a diagnosis. This diagnostic journey, which was paved with numerous studies and analyses, takes up significant time and resources and at times leads nowhere. Approaching distal extremity pain with a complete differential diagnosis, including non-rheumatologic entities, may hasten diagnosis, thus decreasing cost and aiding in earlier initiation of an appropriate therapy. This study aimed to illustrate the requirement to include non-rheumatologic diseases as a differential diagnosis of distal extremity pain by presenting a case of a patient who after years of work up of arthralgia, which was actually attributed to rheumatologic causes, had an inherited metabolic disease.

Case Presentation

A 32-year-old male presented to the clinic with complaints of distal pain in his four limbs, predominantly in the hands, since he was 8 years. Pain was consistent with neuropathic pain because of typical features (burning, tingling, lightning, and stabbing). It increased in intensity when exercising, with febril or subfebril fever, and with an environmental temperature increase. After 6 years of consultation in various pediatric centers, he was diagnosed with growing pains and was treated with non-steroidal anti-inflammatory drugs (NSAIDs), with no response. When he was 12 years, he began to experience gastrointestinal symptoms. In particular, the patient had postprandial pain, early satiety, and intermittent diarrhea. Because of all these symptoms, he had to stop playing sports.

At the age of 15 years, laboratory investigations began targeting rheumatologic causes of his symptomatology. This was because of the persistence of his pain and the appearance of punctiform reddish lesions in the periumbilical and genital regions, which were considered to be petechiae. Varied and repeated studies revealed no autoantibodies, and at 24-h urine examination, the presence of microalbuminuria was only remarkable. When he was 20 years, he had slightly increased creatinine and proteinuria (500 mg/day) levels. His pain persisted, and there was gastrointestinal involvement. After 6 years, a diagnosis of chronic kidney disease of unknown etiology was made despite the absence of a kidney biopsy. He was followed up in our

1 Department of Neurology, Division of Neurometabolism, Foundation for Study of Neurometabolic Diseases (FESEN), Buenos Aires, Argentina

2 Department of Rheumatology, Division of Clinical Medicine, Juan Fernandez Hospital, Buenos Aires, Argentina

3 Department of Nephrology, Division of Clinical medicine, Juan Fernandez Hospital, Buenos Aires, Argentina

4 Department of Medicine, University of Alabama, Birmingham, Alabama, USA

Address for Correspondence: Juan Politei, Department of Neurology, Division of Neurometabolism, Foundation for study of neurometabolic diseases (FESEN), Buenos Aires, Argentina

E-mail: jpolitei@hotmail.com

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clinic for the first time at the age of 32 years, which was 24 years after the onset of clinical symptoms. Unfortunately, he was clinically uremic because of end-stage renal disease, and thus, renal replacement therapy with intermittent hemodialysis was initiated.

During our first assessment for neuropathic pain management, our attention was drawn to his coarse facial features and skin lesions that were compatible with angiokeratomas. A careful examination of family history revealed that his mother and younger brother suffered pain with similar characteristics (only of a lower intensity). Because of the constellation of signs and symptoms and his family history, an analysis of α-galactosidase A enzyme activity on filter paper was requested. The result was 0.1 umol/L/h (normal value: ≥4 umol/L/h). Genetic testing revealed L415P mutation, thus confirming the diagnosis of Fabry disease (FD). Family screening confirmed the same diagnosis for his mother and brother, with the presence of glycosphingolipids deposits in the cornea (cornea verticillata) (Figure 1), periventricular ischemic lesions in the brain MRI (Figure 2), and left ventricular hypertrophy in the echocardiogram. The patient initiated enzyme replacement therapy (ERT) with 1 mg/kg doses of agalsidase beta (Fabrazyme, Genzyme; Boston, USA) every 14 days along with carbamazepine; and significant improvement in neuropathic pain and gastrointestinal symptomatology was observed in at least 70% pain that was measured using a visual analog scale.

Discussion

Fabry disease results from the deficiency of lysosomal α-galactosidase A, generating excessive deposits of glycosphingolipids, mainly globotriaosylceramide (Gl_3). The prevalence of this hereditary X-linked disorder is 1/40,000 live births (1). The Gl_3 deposit can be found in endothelial cells, pericytes, smooth muscle cells of blood vessels, neurons, podocytes, cardiomyocytes, etc. The first symptoms appear in hemizygotes (men) in their childhood, with neuropathic distal pain in all four limbs. Hypohidrosis is another common symptom and can be debilitating and limit participation in sports. Skin lesions, known as angiokeratomas, are a classic and common finding in males with FD. The Gl_3 deposits appear in the cornea during adolescence (forming a pattern known as cornea verticillata). Other symptoms include dysautonomic symptoms, fatigue, and decreased hearing functions. The most severe manifestations, such as renal and heart failure, and stroke without treatment appear in the third decade of life (1).

The pathophysiology of neuropathic pain in FD

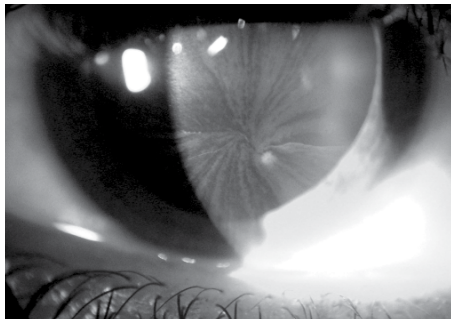

Figure 1. Cornea verticillata in the left eye

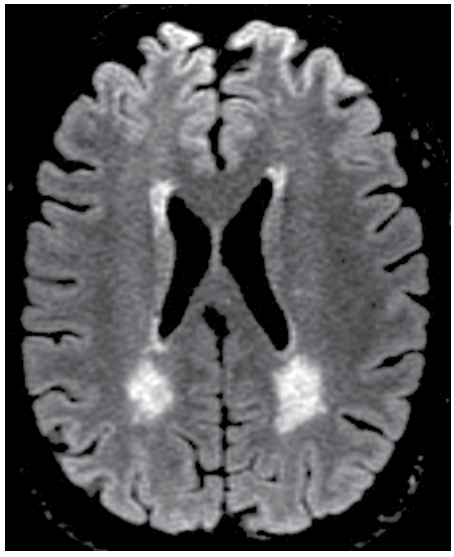

Figure 2. Periventricular ischemic lesions in Fluid-attenuated inversion recovery (FLAIR) sequence

is associated with the small nerve fiber damage (A delta and C) because of ischemia in the vasa nervorum and the deposit of glycosphingolipids in the dorsal root ganglia (2). Sensory neuropathy is experiences as a burning pain in the hands and feet, which is associated with pain crises during fever episodes and when exercising. Recent studies in animal models have demonstrated a significant increase in sodium channels (Nav 1.8) and channels transient receptor potential of vanilloid receptor (TRPV1) because of the axonal damage. These channels are unstable and small increases in temperature results in their activation and the transmission of painful impulses (3).

Previous reports describe FD cases, which were diagnosed after complete serological and histological evaluations by rheumatology, failed to result in a diagnosis of autoimmune disease (4, 5). One of those cases described a male patient, 25 years old, who suffered distal pain since he was 19 years, with no joint morning stiffness or movement limitation, absence of response to NSAIDs, and normal findings in radiography (a). This patient underwent synovial biopsy of the index finger proximal interphalangeal joint, showing a total absence of inflammatory infiltration. Foamy cell deposits were observed at the endothelial level in the subsynovial capillaries and at synovial level. To date, no joint inflammation has been described in patients with FD.

Another factor, which generally leads physicians to suspect rheumatologic diseases in these patients, is the presence of the Raynaud's phenomenon. Raynaud's was described as a manifestation of Fabry in 1992 by Paira et al. (5), and is (6, 7) present in 2 studies was present in 13% and 38% of the study group. The presence of distal cyanosis and pallor in FD is probably because of the abrupt vasoconstriction in areas that were previously hypoperfused regions due to luminal stenosis secondary to the Gl_3 deposit in the vascular wall. Other diseases that can be mistaken for FD include juvenile idiopathic arthritis, rheumatic fever, collagen diseases, systemic vasculitis, sarcoidosis, gout, and fibromyalgia (8, 9).

The presence of autoantibodies has been studied in a series of 33 patients with FD, revealing high prevalence of anticardiolipins (12%). This prevalence is significantly higher than that observed in the general population (10).

There are cases where FD is diagnosed associated with inflammatory diseases, such as rheumatoid arthritis, granulomatosis with polyangiitis, systemic lupus erythematosus, and antiphospholipid syndrome. Although some of these diagnoses have been definitive with a description of mutations associated with classical phenotypes, tissue Gl_3 deposits, and a characteristic family history, in most cases, the diagnosis was made on the basis of decreased α-galactosidase A enzyme activity. To this date, there are an increasing number of false positive diagnoses for FD because of the presence of enzymatic "pseudo deficiencies" as a result of functional polymorphisms and not real mutations. Therefore, when the family history is not typical of FD and the symptoms are not characteristic ones, it is necessary to prove mutations linked to the classical phenotype or the presence of intra-lysosomal Gl_3 deposits in tissue biopsy to reach a definitive diagnosis.

Fabry disease must be included within differential diagnosis of distal extremity pain because it can mimic several rheumatologic diseases. Follow-up studies after several years of ERT in all lysosomal diseases reveal that the prognosis for patients improves when early ERT is initiated. Rheumatologists and immunologists may be the first to encounter patients with FD. If FD is not considered in the differential diagnosis, a missed opportunity for early institution of therapy is likely to occur.

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