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Bone symptoms can be an early manifestation of Gaucher disease implications for diagnosis

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ABSTRACT

Gaucher disease (GD) is caused by mutations in the gene *GBA1,* which encodes for the synthesis of the enzyme lysosomal glucocerebrosidase (GCase). Lack or deficiency of GCase activity causes accumulation of glucosylceramide in the lysosomes of the monocyte-macrophage system in the bone marrow, spleen, and liver, and less frequently in the lungs and the central nervous system; this accumulation results in cell damage and organ dysfunction.

Currently available diagnostic algorithms are based on the well-recognized hematological manifestations (cytopenia and splenomegaly), which are the manifestations most commonly associated with GD. However, 25 to 32% of patients have been found to present with bone signs and/or symptoms as the only or main presenting sign of the disease.

A number of physicians may be unaware of this clinical presentation of GD, and may therefore delay in establishing diagnosis and initiating treatment, when necessary.

We developed an educational program for early detection and diagnosis of GD, which includes a diagnostic algorithm based on GD-related bone manifestations.

We herein report the case of a girl with bone symptoms as the only first manifestation of GD that were mistaken for stress fracture and osteomyelitis, and who was seen by 5 different specialists over a 4-year period before she was accurately diagnosed with GD.

The case presented here shows the usefulness of the educational program for early detection and diagnosis of GD based on bone symptoms.

Key Points

Early treatment is important since it reverses cytopenias and visceromegalies and though it does not totally prevent onset of bone lesions, it decreases their frecuency. Although bone symptoms are present in 25-32% of patients, they are not usually associated with GD. This lack of awareness may cause delays in the diagnosis and start of treatment. We aware of the efficacy in developing an educational program and propose a diagnostic algorithm based on bone manifestations suspicious of GD

Introduction

Gaucher disease (GD) is the most frequent lysosomal disease. It is caused by mutations in the gene *GBA1,* which encodes for the synthesis of the enzyme lysosomal glucocerebrosidase (GCase). Lack or deficiency of GCase activity causes accumulation of glucosylceramide in the lysosomes of the monocyte-macrophage system in the bone marrow, spleen, and liver, and less frequently in the lungs and the central nervous system, and which results in cell damage and organ dysfunction.

It is known that GD has a continuous spectrum of severity, but traditionally three subtypes have been described based on the absence (Type 1) or presence of neurological symptoms (Types 2 and 3).

The most frequent phenotype is type 1 GD (GD1), presenting mainly with hematologic, visceral, and skeletal manifestations. Incidence ranges from 1/40,000 to 1/60,000 in the overall population, and increases to 1/800 births in the Ashkenazi Jewish population.

Clinical suspicion of GD1 is traditionally associated with signs associated with and/or the presence of spleno-hepatomegaly and cytopenia, which have a 30 to 50% incidence as first or presenting symptom, and a 60-95% incidence as the leading symptom at the time of diagnosis[2-7]. Diagnostic algorithms for Gaucher disease are therefore based on these most frequently presenting signs. Of note, these algorithms are mainly used by hematologists [8-10].

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However, 25 to 32% of patients have been found to present with bone signs and/or symptoms as the only or main presenting sign of the disease[11-12]. The lack of awareness of this fact among physicians who have no training in detecting this disease often causes delays in diagnosis, and hence in the initiation of specific treatment when necessary[6,7].

According to the literature, 80% to 95% of patients with GD1, including asymptomatic patients, present with some form of bone involvement at the time of diagnosis. Presenting signs/symptoms may include: Erlenmeyer flask (EM) deformity, decreased bone mineral density (BMD), bone infarcts (BI), osteosclerosis, avascular bone necrosis (AVN), osteolytic lesions, fractures (Fx), bone pain, and bone crises. Between 27 and 63% of patients report a history of bone pain, and 20% report a history of bone crises; this shows that failure to diagnose promptly allows progression of bone involvement. Delayed diagnosis and initiation of treatment lead to the development of irreversible bone complications that affect function, mobility, and quality of life[2,4,13-15].

Enzyme replacement therapy (ERT) involving GCase infusions has been used since 1991, and has been proven to substantially improve cytopenia and visceromegaly in all patients and growth and peak bone mass in children, and to diminish the frequency of irreversible bone complications[16-18]. Early treatment has also been proven to have a beneficial effect on bone pain and bone crises, on bone mineral density, and on the degree of bone marrow infiltration.

In view of the difficulties in timely diagnosis of GD in patients with bone involvement as presenting sign of the disease, we developed an educational program and a diagnostic algorithm based on bone manifestations suggestive of GD. Since 2017, the program has been promoted among health professionals in Argentina through meetings at hospitals, presentations at congresses, and courses on bone diseases.

We herein present the case of a girl with bone symptoms as only manifestation of GD, and who was diagnosed as a result of the implementation of this educational program.

CASE REPORT

We present the case of a term-born female patient with normal growth and development. In her first year of life she was hospitalized for gastroenteritis; during hospitalization she was also tested for celiac disease due to mild anemia and lactose intolerance.

At age 7 years, she complained of pain on right knee flexion. Roentgenograms showed a radiolucent lesion with sclerotic borders in the distal metaphysis of the right femur (Fig. 1), which was interpreted as a stress fracture in the healing phase, and was confirmed by magnetic resonance imaging. Retrospective analysis allowed detecting EM deformity in both femurs, which had previously gone undetected.

At age 10 years 4 months, severe knee pain recurred in the distal third of the right femur, with signs of inflammation, high erythrosedimentation rate and serum C-reactive protein, slight anemia, and leukocytosis. She was hospitalized with presumptive diagnosis of septic arthritis and osteomyelitis.

MRI and bone biopsy were consistent with osteomyelitis. In addition, histopathological examination showed the presence of mononuclear leukocytes and a fair quantity of foamy histiocytes staining positive for CD 68 and negative for CD1 (*BenchMrkGX -Roche)*. Although cultures were negative, IV antibiotic therapy was administered. The patient's recovery was satisfactory.

At age 11 years and 2 months, she suffered an episode of pain in her left lower limb. MRI results were consistent with osteomyelitis of the left distal femoral diaphysis, and myositis in the anterior rectus muscle and posterior muscles. No pathogenic microorganisms were detected in the bone culture, and the histopathological study showed lymphohistiocytic infiltrate and scant macrophages, with no microorganisms or atypical proliferation. Blood cultures were performed twice, and results were negative both times. The condition was diagnosed as chronic recurrent osteomyelitis.

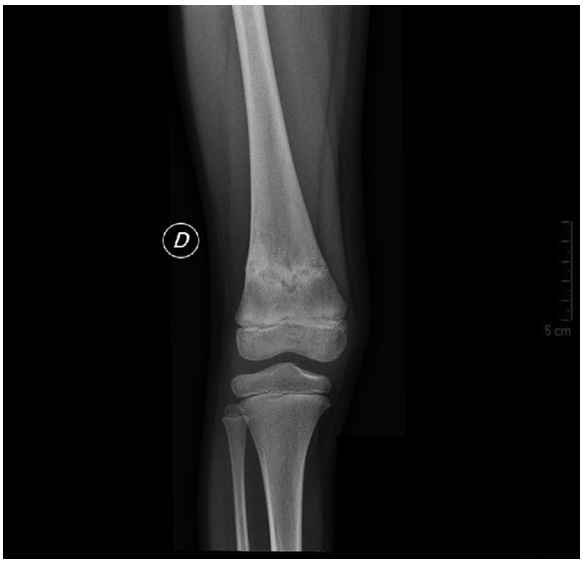

Fig. 1. X-rays showing Erlenmeyer flask deformity in right femur and femoral metaphysis stress fracture in the healing phase.

Following consultation with a specialist in rheumatology who had participated in one of the GD educational talks, her attending physicians saw the need to consider GD1. For this purpose, a dry blood spot sample was collected on filter paper and sent for determination of GCase activity. The results showed enzymatic deficiency, and diagnosis of GD1 was confirmed through the use of an enzyme assay test to measure glucocerebrosidase enzyme activity in circulating leukocytes. Genetic analysis showed the patient's *GBA1* gene genotype was c.1226A>G /RecNcil.

Following diagnosis of GD1, complete bone assessment was performed. Simple radiographs of both femurs showed EM deformity and sclerotic lesions consistent with bone infarcts in the central and distal diaphyseal regions (Fig. 2A), which were confirmed by MRI (Fig. 2B). Bone mineral density of the lumbar spine and total skeleton was normal (Z-score -0.9 and -1.1 respectively). Blood tests showed high levels of serum chitotriosidase (1566 um/l/h; reference range=7.7-110) and ferritin (224 ng/ml; reference range=4.6 – 204), two known markers of GD1 activity. Biochemical parameters of bone and mineral metabolism were normal, and bone remodeling marker levels were normal according to age.

Although no visceromegaly was palpable on physical examination, MRI showed the spleen was 3.2-fold larger than the theoretical normal value for the patient's weight and was consistent with mild splenomegaly, and liver volume was 1.16-fold higher than the normal theoretical volume for the patient's weight; platelet count was $144x10^9/L$ and hemoglobin levels were *11g/L*. ERT with velaglucerase was initiated.

DISCUSSION

The presenting clinical manifestations of GD in the patient shown here were unclear, since the fracture and episodes of bone pain were not accompanied by cytopenia or visceromegaly, which are the more widely recognized features of the disease. This would explain why the patient was seen by 5 different specialists (a pediatrician, a traumatologist, an infectologist, an oncologist, and a rheumatologist) over a 4-year period, before she was accurately diagnosed with GD.

Given that the presence of bone symptoms as initial manifestation of GD is less known, delay in diagnosis in patients with no hematologic alterations or visceromegaly is not infrequent.

According to a retrospective review of the clinical records of 44 patients with documented onset of GD at or before the age of 16 years,

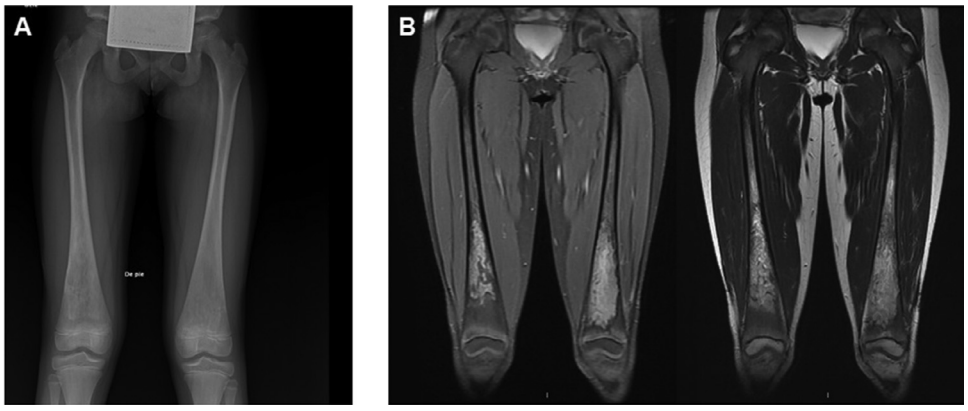

Fig. 2. 2A - X-ray of both femurs showing sclerotic images with ill-defined borders, compatible with sequelae of a bone infarct.
2B. Coronal MRI view of both femurs evidencing changes in signal intensity in the central and distal thirds, compatible with bone infarcts and Erlenmeyer flask deformity.

bone involvement (AVN, BI, bone pain, and misdiagnosis of osteomyelitis) was the second most common clinical presentation, accounting for 32.4% of cases[11].

A more detailed analysis of the history of our patient allows positing that the first fracture at age 7 years may have occurred as a consequence of bone weakening due to infiltration by Gaucher cells. The typical radiographic appearance of EM deformity, which corresponds with the expansion of the bone marrow and subsequent alteration of bone remodeling caused by infiltration of Gaucher cells[14], went undetected at the time.

The ensuing episodes of severe pain in both distal femurs at age 10 and 11 years attributed to osteomyelitis could be interpreted as bone crises, which are characterized by episodes of acute pain that begins as a dull pain that intensifies and becomes severe after 2 to 3 days, and that can persist for 7 to 10 days[15]. It generally occurs together with signs of local inflammation, leukocytosis, and elevated erythrosedimentation, and can present with or without fever, which explains why it is easily confused with osteomyelitis[19,20]. However, toxemia is absent and cultures are negative during a GD-related bone crisis, as occurred with the patient described here. A bone scintigraphy can contribute data for differential diagnosis between osteomyelitis and bone crisis, since increased uptake is observed in osteomyelitis and decreased uptake is observed in acute bone crisis. Nevertheless, severe cases of osteomyelitis can also show a photopenic area (cold osteomyelitis), which is impossible to distinguish from a bone crisis [21]. During an acute bone crisis, MRI shows localized edema in the bone marrow and soft tissues, with increased signal intensity in T2 weighted images, suggestive of hemorrhage of bone [22]. Retrospective analysis of the patient's clinical record and imaging studies performed prior to diagnosis, in addition to the consistently negative bone cultures and the presence of foamy histiocytes observed in the first bone biopsy, allowed identifying signs that could have been a warning signal of the possible presence of GD.

The patient met two criteria proposed in the diagnostic algorithm based on bone manifestations included in our educational program, i.e. osteomyelitis and bone crises.

This observation led to the diagnostic suspicion of GD, and prompted submission of samples for assessment of GCase activity.

It is our understanding that the case presented here shows the usefulness of the educational program for early detection and diagnosis of GD that we have been implementing since 2017.

The educational program mainly targets health professionals who are consulted about a bone disorder: orthopedists, rheumatologists, radiologists, endocrinologists, general practitioners, and pediatricians.

The importance of timely diagnosis of GD in patients presenting bone symptoms lies in the possibility of initiating early treatment that would avoid the irreversible and incapacitating skeletal complications that frequently develop in these patients throughout the natural course of the disease.

To conclude, GD is an infrequent disease that is recognized mainly due to its hematologic alterations. Nevertheless, isolated bone symptoms may be the first clinical manifestation, which makes diagnosis difficult.

The case presented here shows the usefulness of an educational program and diagnostic algorithm based on bone symptoms for diagnosis of GD.

Conflict of interest

Beatriz Oliveri and Diana C González received honoraria from Shire. Emma Ferrari declares no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jechem.2020.04.006.