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Original Article

Evaluation of Bone Mineral Density in Patients with Type 1 Gaucher Disease in Argentina

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Abstract

The purpose of this study was to evaluate the frequency of osteoporosis (OP) in patients with Gaucher disease (GD) in Argentina. GD patients from 28 centers were consecutively included from April 2012 to 2014.

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Conflict of interest: María Larroude received honoraria speakers from Genzyme, Shire, Pfizer, Abbie, Bristol and Elly Lilly. Gabriel Aguilar received honoraria speaker from Genzyme and Abbie.
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Bone mineral density (BMD) was determined by dual X-ray absorptiometry in the lumbar spine and the femoral neck or the total proximal femur for patients ≥20 yr of age, and by whole-body scan in the lumbar spine in patients <20 yr of age. In children, mineral density was calculated using the chronological age and *Z* height. OP diagnosis was determined following adult and pediatric official position of the International Society for Clinical Densitometry. A total of 116 patients were included, of which 62 (53.5%) were women. The median age was 25.8 yr. All patients received enzyme replacement therapy, with a median time of 9.4 yr. Normal BMD was found in 89 patients (76.7%), whereas low bone mass (LBM) or osteopenia was found in 15 patients (13%) and OP in 12 patients (10.3%). The analysis of the pediatric population revealed that 4 patients (9.3%) had LBM and 3 (7%) had OP (*Z*-score ≤ –2 + fractures height-adjusted by *Z*), whereas in the adult population (n = 73), 11 patients (15%) had LBM or osteopenia and 9 (12.3%) had OP. Bone marrow infiltration and the presence of fractures were significantly correlated with the presence of OP ($p = 0.04$ and <0.001, respectively). This is the first study in Argentina and in the region describing the frequency of OP or LBM in GD patients treated with imiglucerase using the official position of the International Society for Clinical Densitometry.

Key Words: Argentina; bone mineral density; Gaucher disease; osteoporosis.

Introduction

Gaucher's disease (GD) is a rare autosomal recessive lysosomal storage disorder caused by a deficiency in the activity of the enzyme acid β-glucocerebrosidase, which produces the accumulation of glucosylceramide in macrophages, that leads to the disease manifestations observed (hematological, visceral, and skeletal damage) *(1)*. Skeletal complications have a high impact on patients' quality of life and affect 90% of them, although there is not always a correlation with bone, hematological and visceral compromise *(1,2)*. Bone pathology affects bone marrow and bone structure *(2)*. Bone marrow infiltration by Gaucher cells causes vascular occlusion and ischemia, producing mineralization alterations, which in turn result in abnormal bone remodeling characterized by osteopenia/osteoporosis (OP), lytic lesions, pathological fractures, vertebral fractures, and aseptic necrosis most common in femoral and humeral heads *(1)*.

Pathogenesis of bone changes is not thoroughly understood, but there are alterations of mineralized bone and the bone marrow *(1)*. In GD, the bone marrow is infiltrated by Gaucher cells, mainly in the spine, the pelvis, and particularly the diaphyseal region of the femur and the humerus *(1)*. Glucocerebroside accumulation triggers macrophage activation, which causes the inflammatory process due to the altered expression of different factors and cytokines such as interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-18; the receptor antagonist of IL-6; the tumor necrosis factor alpha; and prostaglandin E2. In addition, a reduction in the number of T and CD8 lymphocytes has been reported in patients with bone compromise *(1–5)*.

IL-1, IL-6, and tumor necrosis factor alpha release by Gaucher cells might therefore interfere with bone cell activity both in osteoclastic and osteoblastic progenies *(3–5)*. It is also suggested that bone marrow infiltration by Gaucher cells might increase intrabone pressure, causing painful edema and ischemia, and might cause the infarctions and bone crises typically associated with the disease *(3)*.

As a result of medullary osteonecrosis, the death of monocytic cells produces the release of free fatty acids, which, together with calcium ions, form insoluble "calcium soaps" that deposit in the bone marrow and are irreversible. Therefore, there might be an interaction, referred to as osteoimmunology, between immune cells, osteoclasts, and osteoblasts, which could shed some light on the complex system underlying some mechanisms of bone physiopathology that are compromised in GD *(1,2,5)*. Consequently, the most severe bone complications are avascular necrosis, osteopenia/OP, and fractures. These bone complications affect patients' quality of life due to the chronic pain associated with them, which results in disabilities and the need for surgical interventions *(2,3)*. It is important to mention that chronic pain, disability, and need for joint replacement have been remarkably reduced by enzyme replacement therapy (ERT) *(2,3)*.

Osteopenia affects almost 65% of patients with type I GD in patients of the International Collaborative Gaucher Group Registry has an increasing incidence in splenectomized patients. The report presented by Mistry et al *(6)* shows low basal bone mineral density (BMD) in 44% of pediatric patients, in 76% of adolescents, in 54% of young adults, and in 52% of elderly patients, considering a *Z*-score < –1. However, if the cutoff value was a *Z*-score < –2, the one used by the International Society for Clinical Densitometry (ISCD) *(7–10)* for low bone mass (LBM), the percentages were 11.6% in pediatric patients, 41.5% in adolescents, 21.4% in patients between 20 and 30 yr and 21.1% in patients over 30 and under 50 yr.

Although these data are highly valuable, there are no data in Argentina that provide an understanding of the frequency of OP/osteopenia and LBM in GD patients in our setting.

The purpose of the present study was to evaluate OP and LBM or osteopenia frequency in GD patients in Argentina, following the guidelines provided by the ISCD for measuring OP in adult and pediatric patients *(7–10)*, as well as to correlate the presence of OP with different therapeutic goals (TGs) to identify associated risk factors.

Materials and Methods

GD patients from 28 centers located in different Argentine provinces were consecutively included from April 2012