Bone complications in Gaucher disease

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ABSTRACT

Purpose: Gaucher disease (GD; OMIM # 230800) is an autosomal recessively inherited lysosomal storage disease. GD is caused by a deficiency of the lysosomal enzyme, glucocerebrosidase (GBA, also called acid ß-glucosidase or GCase), which hydrolyzes glucosylceramide (GlcCer) into ceramide and glucose. As a consequence of mutations in the *GBA1* gene located on chromosome 1 (1q21) there is an accumulation of GCase substrate, GlcCer, in macrophages. Bone tissue represents a large systemic compartment of the human body, with an active metabolism that controls mineral deposition and removal, and where several factors may play a role. For these reasons, several non-skeletal diseases may influence bone metabolism.

Methods: The present review describes bone skeletal manifestations in the GD and the role of several factors. This manuscript is the result of a review of the literature that focused on the bone manifestations of GD. In particular, relevant studies were identified through a PubMed search strategy. Step 1 consisted of a systematic literature search using the terms: Bone Metabolic Rare Diseases, Hematological Rare Diseases, Gaucher Disease; step 2 involved adding the terms "osteoporosis" or "bone mass", or "bone turnover" or "bone fragility" or "bone deformity", or "bone biomarkers".

Results: The skeletal manifestations of GD include a variety of bone pathologies due to various factors. These pathologies include bone infarcts, avascular bone necrosis, cortical thinning, lytic bone lesions, osteosclerosis and fractures due to osteopenia or osteoporosis, and rarely acute osteomyelitis.

Conclusions: Bone loss in patients with GD should be managed, whenever possible, at or in close liaison with a center that specializes in the diagnosis, management and therapy of metabolic bone diseases. A multidisciplinary approach is important to better understand the complexity and pathogenesis of bone involvement in GD. In this way it will be possible to refine and standardize the diagnostic and therapeutic approaches to bone disease in GD.

KEYWORDS

Bone fragility, rare diseases, osteoporosis, Gaucher disease, lysosomal storage disorder.

Introduction

Definition and pathophysiology of Gaucher disease

Gaucher disease (GD; OMIM # 230800) is an autosomal recessively inherited lysosomal storage disease. In the general population, its incidence ranges from about 1/40,000 to 1/60,000 births, rising to 1/800 in Ashkenazi Jews [1]. GD derives from a deficit of the lysosomal enzyme glucocerebrosidase (GBA, also called acid β-glucosidase or GCase) and is caused by mutations in the *GBA1* gene that encodes the enzyme and is located on chromosome 1 (1q21). As a consequence of these mutations there is an accumulation of GCase substrate, glucosylceramide (GlcCer) in macrophages [1-3]. More than 300 mutations have been described in the *GBA1* gene [2,3].

Structurally, a GlcCer lipid is composed of a glucose molecule bonded to the oxygen atom on carbon 1 of the sphingosine portion of the ceramide. In GD, toxic accumulation of GlcCer lipids occurs in macrophage cells, mainly in the liver, spleen and bone marrow. These macrophage cells are typically enlarged, with eccentric nuclei and condensed chromatin, and heterogeneous "crumpled tissue paper cytoplasm. This appearance is due to the presence of GlcCer aggregates in characteristic twisted fibrillar arrangements that can be visualized using electron microscopy (Gaucher cells) [3]. Gaucher cells result from the transformation of macrophage cells through a characteristic fully polarized activation (M1subpopulation) and through alternative pathway (M2subpopula tion) [3,4]. These specific phenotypes depend on the specific tissue and microenvironment in which the macrophages are found. In GD, there is activation of M1 and M2 by numerous cytokines and chemokines which are expressed in greater quantities in the plasma of patients with the disease, and which could be implicated in the pathogenesis of bone alterations. Only some of these molecules are expressed by Gaucher cells. This is the case of chitotriosidase and CCL18, which therefore constitute specific markers [3].

GlcCer is also the substrate of an alternative pathway in which a ceramidase transforms it into glucosylsphingosine (or lyso-glucosylceramide), which then diffuses into fluids due to its reduced hydrophobicity. This route is favored in cases of GCase deficiency. In the cytoplasm, glucosylsphingosine is metabolized by a second active GCase at neutral pH (encoded by the *GBA2* gene), which produces sphingosine and

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then sphingosine-1-phosphate (S1P) [3]. Sphingosine could be particularly toxic to bones. Furthermore, the accumulation of glucosylsphingosine can cause neuronal dysfunction and death, resulting mainly in GD-related neurological symptoms [5]. Glucosylsphingosine is normally absent from the human brain but is detectable in the brains of patients with neurological lesions related to GD. Glucosylsphingosine could serve as a source of S1P, influencing the differentiation, migration and survival of several cell types, including lymphocytes and macrophages [3]. Figure 1 shows the metabolic pathways of the GlcCer accumulation due to glucocerebrosidase deficiency.

Phenotype of Gaucher disease

The phenotype of GD is variable, but three clinical forms have been identified: type 1 is the most common and typically causes no neurological damage, whereas types 2 and 3 are characterized by neurological impairment. However, these distinctions are not absolute, and it is increasingly recognized that neuropathic GD represents a phenotypic continuum, ranging from extrapyramidal syndrome in type 1, to hydrops fetalis in type 2 [3].

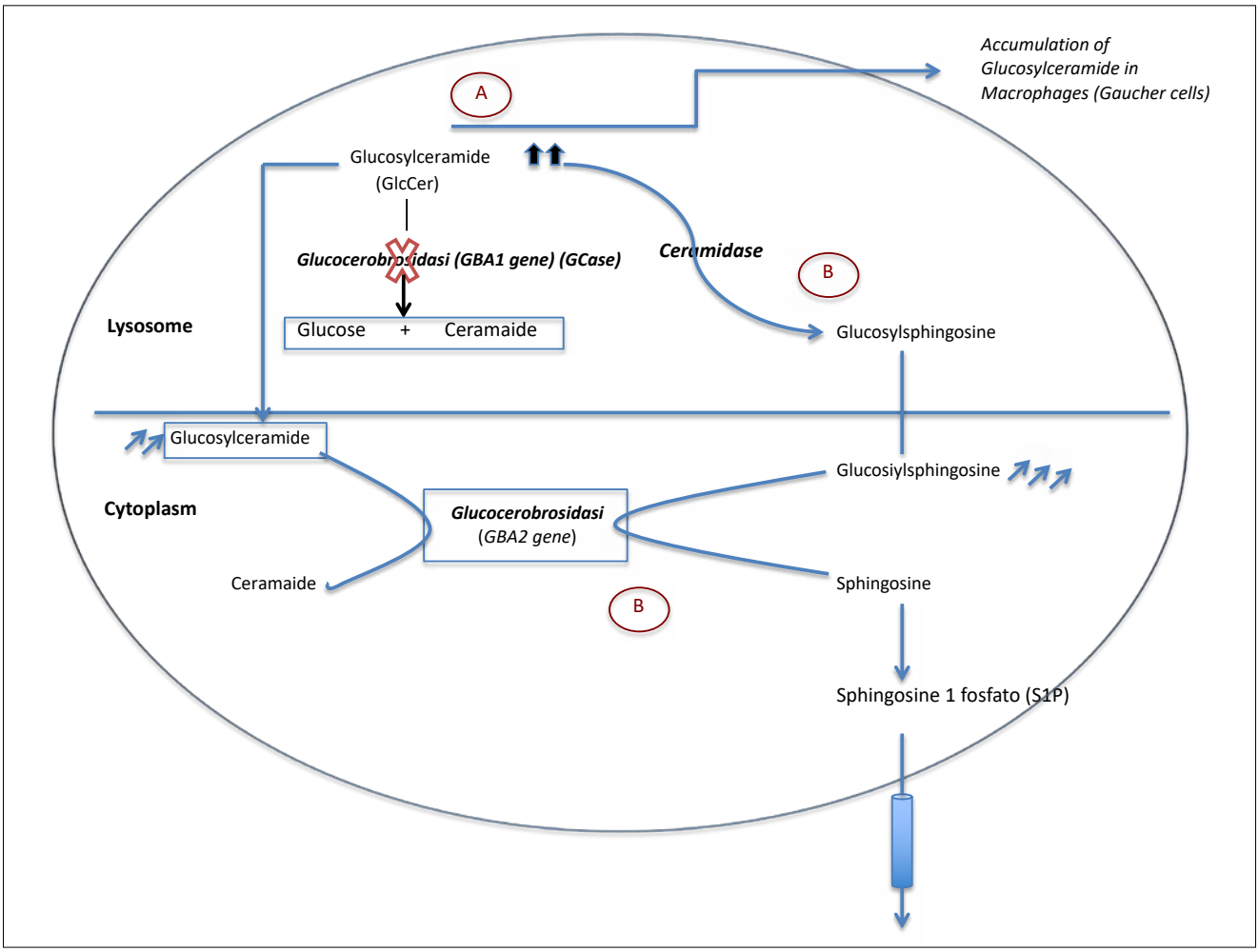
According to a review by Nalysnyka *et al*. [6], the standardized birth incidence of GD in the general population ranged from 0.39 to 5.80 per 100,000; prevalence ranged from 0.70 to 1.75 per 100,000. Time from onset of GD symptoms to clinical diagnosis was highly variable, with median delays of up to 7 years reported [6]. The carrier frequency among Ashkenazi Jewish (AJ) individuals is estimated to be 6%, compared with 0.8% in non-Jewish populations, and the GD prevalence in the AJ population is estimated at 1 in 850 (118 per 100,000) compared with 1-2 per 100,000 in non-Jewish populations [6,7].

Type 1 Gaucher disease

Patients with non-neuronopathic GD (type 1 - GD1) (ORPHA 77259), the most common form, present with hepatomegaly, splenomegaly, anemia, bleeding tendencies, thrombocytopenia, skeletal disorders, growth retardation and, in severe cases, lung disease.

The median age at diagnosis ranges from 10 to 20 years [3]. Although the overall mean age at onset of patients in the Gaucher Registry (run by the International Collaborative Gaucher Group) is 20.4 years, the majority (56%) of patients experi-

Figure 1 Metabolic pathway of the glucosylceramide (GlcCer) accumulation due to glucocerebrosidase (GCase) deficiency. **A**: Accumulation of its substrate in the cell lysosome. GlcCer forms fibrillar aggregates that accumulate in macrophages and give the cell a "crumpled tissue paper" appearance (Gaucher cells). **B**: Alternative metabolic pathway of the GlcCer accumulation due to GCase deficiency. GlcCer is transformed via an alternative ceramidase pathway into glucosylsphingosine which is degraded by cytoplasmic GCase2 (*GBA2* gene) to S1P.



enced onset before the age of 20. However, this Registry primarily includes symptomatic and treated patients, and thus the mean age is probably skewed. Two thirds (68%) of this group were diagnosed before they were 10 years old, and almost half (48%) before the age of 6 [3,8]. Splenomegaly is observed in more than 90% of patients and is sometimes massive, with a spleen weighing up to several kilograms and causing abdominal pain or distension. Indeed, it may be the only clinical sign, leading to unnecessary tests if GD is not considered.

Bone manifestations include bone infarcts, avascular bone necrosis, lytic lesions, osteosclerosis, fractures due to osteopenia or osteoporosis, and rarely acute osteomyelitis. Bone pain of varying intensity, fractures and progressive joint collapses can cause reduced mobility, impaired performance status, and increased morbidity [9]. Bone involvement in GD is known to be common: according to the literature it occurs in approximately 75% of patients with GD type 1 (GD1) [10]. Data from the Gaucher Registry indicated that the frequency of any bone involvement in GD1 patients is more than 90% [10].

Type 2 Gaucher disease

GD type 2 (type 2 - GD2) (ORPHA77260) is characterized by early and severe neurological impairment starting in children aged 3 to 6 months, and by systemic involvement with hepatosplenomegaly. The triad of neck and trunk stiffness (opisthotonus), bulbar signs (particularly severe swallowing disorders) and oculomotor paralysis (or fixed bilateral strabismus) is very suggestive of the disease. There is no bone involvement in GD type 2. Death generally occurs before the third year of life [3].

Type 3 Gaucher disease

GD type 3 (type 3 - GD3) (ORPHA77261), also called juvenile or subacute neurological GD, is characterized by visceral manifestations as described in GD1, usually combined with oculomotor neurological involvement, which in most cases appears before the age of 20 [3].

Patients with type-1 GD - but also carriers of mutations in *GBA1* - have been found to be predisposed to developing Parkinson's disease, and the risk of neoplasia associated with the disease is still a topic of debate [3].

The frequency of hypergammaglobulinemia and the presence of monoclonal Ig in GD are two factors that promote the emergence of multiple myeloma; the incidence of myeloma appears to be increased in GD, with a relative risk of at least 5.9 (95% CI: 2.8-10.8) [3]. There is also an increased relative risk of lymphoma [3] and of solid cancer (hepatocellular carcinoma [3], melanoma, and pancreatic cancer [3]), but there is less evidence than for hematological cancers.

The 3 main GD phenotypes and the possible comorbidities are listed in figure 2.

Bone diseases in Gaucher disease

The skeletal manifestations of GD include a variety of bone pathologies due to various factors. They include bone infarcts, avascular bone necrosis, cortical thinning, lytic bone lesions, osteosclerosis and fractures due to osteopenia or osteoporosis, and rarely acute osteomyelitis. Primary changes are likely to be due to altered cytokine expression or increased local pressure [9,11]. Changes in cytokines, including inflammatory mediators, such as interleukin (IL) -1, IL-6 and tumor necrosis factor alpha, consequently, affect the activity of osteoclasts and osteoblasts [9]. In particular, changes in some cytokines that increase bone resorption by osteoclasts and reduce bone formation by osteoblasts appear to be relevant for the development of osteoporosis in GD [9,12]. Furthermore, the increased production of sphingosine could be particularly toxic to the bones. Second-

Figure 2 The 3 main GD phenotypes and their possible comorbidities.

TYPE I: NOT NEUROLOGICAL, ADULT	TYPE II: ACUTE, NEUROLOGICAL, CLASSICAL / NEONATAL	TYPE III: NEUROLOGICAL SUBACUTE, JUVENILE
	(<5% of cases in most countries, but up to 20% in some cohorts)	
Tiredness (50%) Organomegaly [Splenomegaly (90%); Hepatomegaly (60-80%)] Tendency to bleed Thrombocytopenia Anemia Bone involvement (90% in GD1) Growth retardation Pulmonary and renal involvement	Stiffness in the neck and trunk Bulbar signs Paralysis of the oculomotor nerves (fixed bilateral strabismus)	Manifestations of GD1: - IIIa; neurological > visceral phenotype - IIIb: neurological < visceral phenotype

COMORBIDITIES OF GAUCHER DISEASE

Increased incidence of malignancies (multiple myeloma and lympho-proliferative diseases)
Impaired glucose tolerance
Neurological disorders (Parkinson's disease)

ary changes, such as bone infarcts, can evolve from complex pathological mechanisms including changes in cytokine release, impaired vascularity, and increased local pressure due to extensive glucocerebroside accumulation [13]. Clinically, these pathologies are acute events often accompanied by severe bone pain. Furthermore, in GD there is alteration of the immunecell-osteoclast/osteoblast interactions [9]. In addition, a decrease in the number of CD8+ T lymphocytes have been reported in patients with bone involvement with an alteration of the CD4+/CD8+ T cells ratio [14]. Cathepsin K has been identified as the major expressed osteoclast protein and it is highly active in the cleavage of bone matrix proteins, type 1 collagen and osteonectin; its role in bone resorption, modeling and turnover is clearly demonstrated by the occurrence of an osteopetrotic syndrome in mice homozygous for an interrupted allele of cathepsin K [15,16].

Growth retardation

Symptomatic GD is often accompanied by retarded growth and also delayed pubertal development. Although bone growth can accelerate with the onset of puberty, some children continue to have a short stature through to adulthood. After the advent of enzyme replacement therapy (ERT), a reduction in growth retardation in childhood and an improvement in bone mineral density (BMD) have been observed [15]. ERT was started before the growth plate closed and reached the expected height [17].

Erlenmeyer flask deformity

Erlenmeyer flask deformity describes a distinct abnormality of the distal femurs or other tubular bones and particularly the proximal tibia. It occurs before puberty, develops progressively and is present in 80% of adult patients. Radiologically it is characterized by a constriction of the diaphysis, flaring of the metaphysis and progressive enlargement of the metaphyseal area [15,17].

Focal osteolytic lesions

These lesions are common in GD and can be combined with other localized bone alterations such as cortical thinning. The bone has a "worm-eaten" appearance with radiologically rarefied cortex and dentate endosteum [3].

Osteonecrosis

Osteonecrosis is the main and most disabling skeletal manifestation secondary to bone infarction. The most affected areas are the femoral head, the proximal humerus and the vertebral bodies. It is an irreversible manifestation and causes joint collapse and pathological fractures. Furthermore, in patients with GD, bone fractures can also present with sudden onset of localized pain, tenderness, erythema and swelling. Such acute episodes of severe bone pain are often accompanied by fever, increased leukocytes, and accelerated erythrocyte sedimentation rate. This acute focal bone involvement of GD, also called "bone crisis", can result in aseptic osteomyelitis. True osteomyelitis is rare in GD, although clinical differentiation between aseptic and pyogenic osteomyelitis is difficult or even impossible at onset. Negative blood cultures and aspirates can rule out pyogenic osteomyelitis [9]. Finally, associated with bone infarction, osteosclerosis may be present, often accompanied by severe (irreversible) pain. It can result from: 1. dystrophic calcification of the necrotic bone marrow; and 2. increased activity of the periosteum above the necrotic area in cases of extensive infarction [18,19].

Osteoporosis

Osteopenia and osteoporosis are common in patients with GD, occur at all ages and in both sexes, and progress with age [3, 13,21]. Low bone mass can be diffuse or localized, can affect both cortical and trabecular bone, and is suggested to occur near Gaucher cell infiltration sites [19]. Reduced BMD can be detected as early as 5 years of age in patients with GD1, although it is more pronounced during adolescence [21]. Failure to achieve optimal bone mass is likely to affect peak bone mass and may contribute to osteoporosis and increase the risk of pathological fractures and joint collapses during adolescence [21,22]. Further studies [23-26] confirmed these results in patients with GD showing a decrease in BMD at various sites (lumbar spine, neck, trochanter and distal radius). Furthermore, Khan *et al*. also indicated that, in the management of patients with GD1, a spinal DXA Z-score ≤1 should be a significant trigger for a therapeutic intervention aimed at maintaining BMD above this value [27]. From the metabolic point of view, Giuffrida *et al*. [29] in a meta-analysis observed that studies involving bone biomarkers in patients with GD show variable results that currently do not support their routine use either for clinical assessment of bone status as an indication for initiation of therapy, or for monitoring of response to therapy, suggesting that there is a need for greater understanding of bone biomarkers and their relationship to bone manifestations of GD [28]. Studies have shown positive effects of ERT and substrate reduction therapy on bone crisis frequency, bone pain and BMD [29-31]. Finally, a few studies on the effects of bisphosphonates (BP) in GD patients with osteopenia/osteoporosis have been reported in the literature [32], but with heterogeneity of results and study design. Furthermore, no data on fracture reduction are available so far and the pathophysiology of GD bone complications is not well understood [9].

Recently, an international group of doctors, experts in GD, addressed various aspects of bone pathology in the disease, underlining the heterogeneity of its clinical manifestations and the need to perform instrumental examinations. Their conclusions are here summarized.

- Evidence suggests that although the pathology of bone marrow disease and bone tissue are etiologically linked, MRI and DXA bone densitometry monitoring should be considered separately. MRI and DXA provide useful information on the current state of the disease and the likelihood of future events such as heart attack, fractures, etc.
- The authors suggest performing serial DXA scans using the same device in: patients aged <50 years (including premenopausal women), evaluating the Z-score with a check once every 2–4 years; in patients aged >50 years and postmenopausal women, evaluating the T-score, and in patients under corticoid therapy with a check every 1–2 years. The authors maintain that during therapy it is important to allow at least 12 months between BMD evaluations. Finally, a total body DXA in children older than 5 years has been indicated.

- MRI is the gold standard for monitoring bone involvement in GD patients, taking into account the patient's age. Under 19 years, the authors suggest including the tibiae (bone marrow in tibiae is converted to fatty marrow at around 9 years of age). Below the age of 9, it is very difficult to assess red marrow infiltration. Although plain radiography is not as sensitive or precise as MRI or DXA, it can provide useful and clinically meaningful information in locations where MRI and DXA are not available. In this instance children should be assessed annually and the radiograph evaluated by an orthopedist or radiologist experienced in GD. The utility of whole-body MRI, proton MR spectroscopy and QCSI is theoretical because the availability of these modalities is limited.
- In addition to drug therapy, it is important to pay attention to lifestyle factors (ensuring appropriate calcium and vitamin D intake, and physical exercise, and avoiding smoking and excessive alcohol consumption).
- Further studies are needed to understand the relationship between an improvement in bone disease and a change in the risk of bone events. Since reduced BMD is associated with an increased risk of fractures, we need to understand whether the improvement translates into a clinical effect [17].

Conclusions

Although GD it is the most common of the lysosomal storage diseases, it remains rare and most cases present a gradual-onset phenotype, which explains its delayed diagnosis. The majority of lysosomal storage diseases have bone involvement. This occurs frequently in GD patients, in whom it is one of the most debilitating complications, reducing the quality of life of patients [33]; however, in GD patients, the pathogenic basis of the bone complications is not fully understood [19]. The therapeutic advances of recent years, including the development of new enzymes and a new substrate inhibitor, represent significant progress, but research efforts must be maintained

Bone loss in patients with GD should be managed, whenever possible, at or in close liaison with a center that specializes in the diagnosis, management and therapy of metabolic bone diseases. A multidisciplinary approach is important to better understand the complexity and pathogenesis of bone involvement in GD. In this way it will be possible to refine and standardize the diagnostic and therapeutic approaches to bone disease in GD.

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