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# Re-evaluation of bone pain in patients with type 1 Gaucher disease suggests that bone crises occur in small bones as well as long bones

Hagit N. Baris [a,b,*], Monika Weisz Hubshman [c,d], Zvi Bar-Sever [d,e], Liora Kornreich [d,f], Vered Shkalim Zemer [d,g], Ian J. Cohen [c,d,g]

[a] The Genetics Institute, Rambam Health Care Campus, Haifa, Israel
[b] Rappaport School of Medicine, Technion, Haifa, Israel
[c] The Raphael Recanati Genetics Institute, Rabin Medical Center, Children's Medical Center of Israel, Petah Tikva, Israel
[d] Sackler Faculty of Medicine, Tel Aviv University, Israel
[e] Department of Nuclear Medicine, Israel
[f] Pediatric Radiology Schneider Children's Medical Center of Israel, Petah Tikva, Israel
[g] Department of Pediatric Hematology-Oncology, Schneider Children's Medical Center of Israel, Petach Tikva, Israel

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ABSTRACT

Bone crises in type 1 Gaucher disease are reported in long bones and occasionally in weight bearing bones and other bones, but rarely in small bones of the hands and feet. We retrospectively examined the incidence of bone pain in patients followed at the Rabin Medical Center, Israel, before and following the initiation of enzyme replacement therapy (ERT) and evaluated them for bone crises. Of 100 type I Gaucher disease patients, 30 (30%) experienced one or more bone crises. Small bone crises represented 31.5% of all bone crises and were always preceded by crises in other bones. While the incidence of long bone crises reduced after the initiation of ERT, small bone crises increased. Almost 60% of patients with bone crises were of the N370S/84GG genotype suggesting a greater susceptibility of N370S/84GG patients to severe bone complications. These patients also underwent the greatest number of splenectomies (70.6% of splenectomised patients). Splenectomised patients showed a trend towards increased long and small bone crises after surgery. Active investigation of acute pain in the hands and feet in patients in our cohort has revealed a high incidence of small bone crises. Physicians should consider imaging studies to investigate unexplained pain in these areas.



## 1. Introduction

Type 1 (non-neuronopathic) Gaucher disease is the most common clinical variant of Gaucher disease, a rare inherited lysosomal storage disorder affecting around one in every 40,000–60,000 people in the general population and approximately one in every 800 people of Ashkenazi Jewish origin [1,2]. Gaucher disease is characterised by mutations in the gene for beta-glucocerebrosidase (GBA) causing reduced beta-glucocerebrosidase activity, which results in the accumulation of glucocerebroside within macrophages. These 'Gaucher' cells can be found in the liver, spleen, and bone marrow, and are associated with widespread disease. Classical signs and symptoms of type 1 Gaucher disease generally include anaemia, thrombocytopenia, hepatosplenomegaly and skeletal disease [3] but there is great variability between patients even with the same genotype in terms of age of clinical presentation, organs affected and rate of progression [4].

The majority of patients with type 1 Gaucher disease have radiological evidence of skeletal involvement, most commonly bone marrow infiltration by Gaucher cells, osteopenia and bone remodelling abnormalities (the Erlenmeyer flask deformity) and, less commonly, infarction, avascular necrosis (AVN) and fractures [3]. Skeletal complications are a significant source of morbidity and reduced quality of life [5]. Patients may experience general bone pain, intensely painful episodes of pain known as bone crises, reduced mobility as a result of pathological fractures, osteonecrosis and joint collapse [6].

Bone crises, experienced by approximately 33% of untreated patients [3], are amongst the most debilitating of bone manifestations and are thought to be precursors to osteonecrosis, a potentially disabling bone manifestation in Gaucher disease affecting predominantly the femoral head, proximal humerus and vertebral bodies, which can result in fracture, AVN and joint collapse [6,7].

Bone crises are acute episodes of severe pain, which typically begin with regional dull, aching pains that become extreme over about three days. Intense pain may continue for 7–10 days followed by attenuation to a dull ache that can persist for several weeks [8]. Bone crises are typically associated with one or more of the following; warmth at the site of pain (with or without systemic fever), an elevated white blood

* Corresponding author at: The Genetics Institute, Rambam Health Care Campus, Haifa, Israel.
*E-mail address:* hb_feldman@rambam.health.gov.il (H.N. Baris).

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cell count and a raised erythrocyte sedimentation rate [9]. A radionuclide bone scan typically shows decreased radionuclide uptake at the involved site, followed by increased uptake six weeks later [7]. MRI in acute bone crises reveals localised oedema of the bone marrow and soft tissues with increased signal on T1-weighted images at the site of the crisis, suggestive of haemorrhage [6]. Several weeks after the bone crisis has subsided, plain radiology typically shows very clear periosteal elevation [10].

Treatment has involved immobilisation, hydration and attempts at pain management. The pain of bone crises can be severely debilitating. A confirmed diagnosis of bone crises (with bone scan or MRI) may, therefore, warrant consideration of adjunctive therapies. Although pain is often unrelieved by narcotics [10], it may be aborted within hours by oral high dose prednisone [9]. Symptoms of bone crises may mimic those of osteomyelitis and it is imperative to rule out osteomyelitis especially if therapy with high dose steroids is contemplated. A bone scan generally shows increased radionuclide uptake in osteomyelitis while Gaucher disease bone crisis shows decreased uptake in the acute phase [10]. However, in severe cases of osteomyelitis a scan may show a photopenic area (cold osteomyelitis) that is impossible to distinguish from a bone crisis. Toxaemia is absent in a Gaucher disease bone crisis and blood cultures are negative [6].

Enzyme replacement therapy (ERT) (which became available in 1991) with alglucerase or imiglucerase (Genzyme, a Sanofi company, MA, USA) may achieve significant improvements in Gaucher disease-related bone status, although it is recognised that for some aspects of bone disease, such as bone mineral density, the response to treatment may be slower than that of visceral and haematological parameters [11]. The occurrence of bone crises has reduced significantly following 2–3 years of treatment with alglucerase or imiglucerase [8,12–15], but the risk of bone crises may not be eliminated; some patients experience bone crisis for the first time or suffer recurrent bone crises despite treatment and despite having apparently stable disease [8,9,12–15]. Before the ERT era bone crises of long bones were a known precursor of pathological fracture [16,17]. There is a lack of long-term data on bone outcomes, especially the incidence of bone crises, for alternative ERTs, such as velaglucerase alfa (Shire Human Genetic Therapies; approved by the FDA in 2010) or taliglucerase alfa (Pfizer; FDA approved in 2012). Preliminary evidence for miglustat substrate reduction therapy (Actelion, approved by the FDA in 2003) has shown no new bone crises for a limited period of one to two years in patients previously treated with imiglucerase [18–20]. A second substrate reduction approach, eliglustat, which was approved by the FDA in August 2014, has shown no bone crises, no symptomatic infarctions, and improvement in 2 preceding infarcts (in one patient) after 4-year follow-up of a phase II study in 19 treatment-naïve adults [21,22].

Although bone crises typically occur in long bones they may also occur in other bones such as the skull or pelvis. Collapse of weight bearing bones may occur especially of the vertebral bodies, calcaneus and femoral head [16] and 'romantic fractures' of the ribs have been described [23]. Bone crises in the small bones of the hands and feet also occur but have been described rarely; they have been reported previously in studies of the hands [24] and feet [25] and in series of bone scans in Gaucher disease [7].

In this study, we retrospectively examined the incidence of bone pain and bone crises, including small bone pain, in patients followed at the Rabin Medical Center, Petah Tikva, Israel, before and following the initiation of ERT.

## 2. Patients and methods

The clinical records of 100 patients with confirmed diagnosis of type 1 Gaucher disease followed at the Rabin Medical Center, Israel were examined retrospectively for bone crises. The location of bone crises was defined as follows: in long bones (femora, fibulae and tibiae and excluding patellae); weight-bearing bones (spine, pelvis, calcaneus); other bones (such as clavicle, skull and ribs); and small bones (all small bones of the hands and feet not including the calcaneus). Patients' spleen status [25–28] and history of pregnancy [29,30] were documented as possible risk factors for exacerbated bone disease.

For patients under the Center's care at the time of bone crises, bone crises were confirmed by radionuclide bone scan [7] or MRI imaging (or both) (see Figs. 1–4). For patients with a history of bone crises referred by other physicians, bone crises were considered to have occurred if imaging showed evidence of old foci of avascular necrosis supported by adequate documentation from the referring physicians (it is acknowledged that this definition, published previously by our group and others [6,7], is not universally accepted by the Gaucher community). Self-reports by patients were also included if they were considered by the authors to be clinically authentic although they may not have been associated with specific dates of occurrence or with any evidence from imaging. For interventions thought to impact the frequency of bone crises, such as ERT or splenectomy, results have been delineated by three categories, 'before', 'within one year' and 'following one year or more' since the intervention. This is to reduce uncertainty when precise dates have not been recorded and also to introduce an interval between the intervention and when the impact of the intervention may be likely to be observed. For example, although the effects of treatment on visceral parameters might be expected within one year, the effects on bone are thought to be slower and may take several years to become apparent [15,31]. Similarly, a median interval of 4.4 years between splenectomy and the onset of osteonecrosis has been reported [28].

Institutional Review Board approval was obtained for clinical follow-up of patients and informed patient consent was obtained before molecular analyses.

## 3. Results

### 3.1. Occurrence of bone crises

Of 100 type I Gaucher disease patients, 30 patients (30%) (19 males and 11 females) experienced one or more bone crises. Overall, 26 patients had one or more date-documented events (total of 124 events); and 4 patients had one or more non-date-documented (NDD) events. The clinical and demographic characteristics of patients with bone crises are shown in Table 1S (Supplementary material). Table 2S shows the year, frequency and site of bone crisis events.

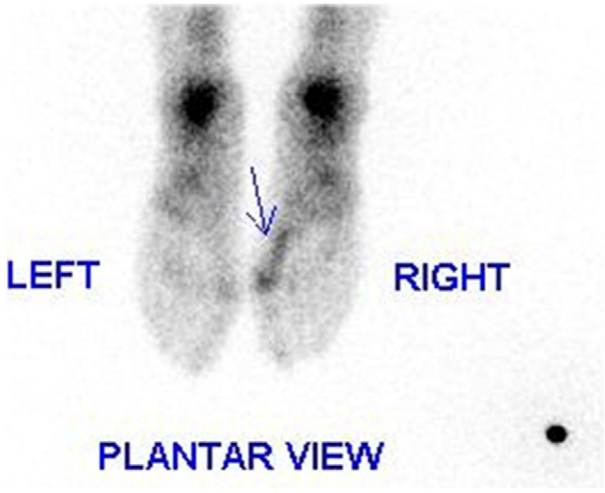


**Fig. 1.** A plantar view of the feet from a follow-up Tc-99m MDP bone scan shows new tracer uptake along the first metatarsus bone of the right foot. The patient (#9) was asymptomatic at the time of imaging and had no history of trauma to his feet. Findings are due to reparative changes following bone infarction that occurred several weeks prior to the scan.