

# Bone pathology of Gaucher disease

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**G**aucher disease (GD) is a congenital fault of the metabolism due to a deficiency in the lysosomal enzyme glucocerebrosidase, also called acid beta glucosidase. This enzyme deficit results in the accumulation of non-metabolised substrate in the lysosomes of various cell lines of the monocyte-macrophage system. The deposit of non-degraded material, a glucocerebroside called glucosylceramide, is an intermediate metabolite in the synthesis and breakdown of glucosphingolipids. These macrophages laden with lipids, called "Gaucher cells", are involved in the pathogeny of the disease<sup>1</sup>. GD is a sphingolipidosis, which constitutes the most frequent lysosomal deposition disease. GD is a multiethnic disorder which is inherited in a recessive autosomic way<sup>1</sup>. The Gaucher Registry is the largest co-operative observational register in the world. Up to January 2007, 4,585 patients from 56 countries had been registered ([www.gaucherregistry.com](http://www.gaucherregistry.com)). It is estimated that there are currently around 300 diagnosed cases in Spain, although it is calculated that there are many more. In the majority of case, the molecular basis of the disease is made up of mutations in the gene GBA (Glucocerebrosidase beta acid) located in chromosome 1 (1q21) which codes for glucocerebrosidase. GD has three clinical forms, and in all of these there is bone, bone medullar and visceral affectation. The Neuronopathic Gaucher Disease Task Force of the European Working Group on Gaucher Disease classifies the disease as: type 1, or non-neuropathic; type 2, or acute neuropathic; and type 3, or chronic neuropathic<sup>2</sup>. Type 1 GD is the most common, making up 94% of all cases. Type 2 GD is the form called infantile cerebral. Type 3 GD is very rare and is only seen in the Norrbottnian region in the north of Sweden. For this reason we are always here referring to type 1 GD. GD, as with other rare diseases is characterised by being multisystemic. Notable among its multiple clinical manifestations are osteopenia, bone pain, bone fractures, anaemia,

thrombopenia, haemorrhages, delayed growth, hepatomegaly, splenomegaly and changes in liver function tests. The prognosis of GD depends on the degree of affectation of these clinical manifestations. GD is a disease which starts in infancy but which is not usually diagnosed until the age of 16 years<sup>2</sup>. Even in those patients diagnosed as adults, the signs and symptoms begin in infancy<sup>3</sup>. This is why each patient is different in terms their age of presentation, symptomology, diagnosis and progression of the disease. Although there is a fulminant presentation form in infancy, the disease may be asymptomatic and diagnosed by chance in adults, in whom it usually takes an insidious and progressive course. Despite being treated as a hereditary disease, the diagnosis of type 1 GD is carried out in 74% of cases at an adult age. And 10% of cases of GD are even diagnosed at over 50 years of age. If it is not brought to mind, it is almost impossible to diagnose. It initially presents as a combination of symptoms such as bone pain, haematomas and asthenia. For this reason it is usually wrongly labelled as a non-specific viral infection, "growing pains", a crisis of acute bone pain with local inflammation and/or fever with necrosis in the hip categorised as Perthes disease, accidental fractures, recurrent epistaxis due to non-specific alterations in coagulation and splenomegaly. The patient with established type 1 GD is usually pallid, with a distended abdomen, thin extremities and valgus knees. They may die in the aftermath of severe bone disease, haemorrhages, infections, liver insufficiency or lung complications. In addition, these patients also have a higher risk of multiple myeloma.

The skeletal affectations are accompanied by osteopenia, bone pain crisis similar to those of drepanocytic anaemia, osteolytic lesions, pathological fractures, vertebral compression and osteonecrosis (avascular necrosis) of the proximal and distal extremes of the femur, and the proximal extremes of the tibia and humerus<sup>4</sup>. The data in the International Register of GD from 1,698 patients shows that 94% have type 1 GD, and of

these, 63% suffer from bone pain, 33% have a crisis of bone pain, 8% have required joint replacement and 94% had radiological evidence of skeletal disease. A radiological study may prompt a diagnosis of GD and/or its complications. X-rays of the large bones can show in 46% of cases a deformity in the Erlenmeyer flask in the distal extreme of the femur, caused by anomalous metaphyseal remodelling<sup>3</sup>. This failure is suggestive but not pathognomonic, requiring a differential diagnosis from osteopetrosis, Nieman-Pick disease, heavy metal poisoning and fibrous dysplasia. The X-rays may also show fractures and lytic lesions, which are present in 15% and 8%, respectively, in the patients on the GD Registry<sup>3</sup>. Bone densitometry with DXA shows generalised loss of bone mass in all the patients<sup>5</sup>. Osteopenia is present in 42% of the patients on the GD Registry<sup>3</sup>. Gammagraphy with technetium detects the presence of ischemia during bone pain crises. The infiltration of the bone medullar, present in 40% of the patients, can be detected through magnetic resonance. Bone infarcts and osteonecrosis, present in 25% of cases, can also be detected through magnetic resonance<sup>3</sup>. The bone affectation can also cause an increase in acid phosphate. The diagnosis is based in a high index of suspicion based on clinical, radiological and laboratory signs described above. The confirmation diagnosis is based on the demonstration of a deficit in the activity of the glucocerebrosidase enzyme (beta glucosidase) in the leukocytes of peripheral blood (enzymatic diagnosis). It is also possible to carry out a study of the mutations of DNA in the cells of the patient, which serve to classify and diagnose their carrier status. They also serve to predict clinical signs and to identify familial cases and heterozygote carriers. The evolutionary control of GD includes blood analysis (chitotriosidase, haemogram and haematic biochemistry), bone densitometry, following the recommendations of the ICGG ([www.gaucherregistry.com/](http://www.gaucherregistry.com/))<sup>3</sup>. Chitotriosidase is a marker for the stimulation of the macrophages. It is increased in Gaucher patients and reduces in response to replacement therapy. It is used in the diagnosis and follow up of the disease. GD is one of the few rare diseases which has a treatment.

This consists of treatment to replace the deficient enzyme, glucocerebrosidase, through the administration of recombinant glucocerebrosidase imiglucerase (imiglucerase)<sup>3</sup>. Early treatment can prevent or delay the progression of bone, and other, complications, hence the importance of early diagnosis of the disease. Once developed, osteosclerosis, osteonecrosis and vertebral compression are irreversible<sup>3</sup>. In summary, GD is a rare multisymptomatic disorder which requires a high index of suspicion on the part of the doctor. Given that it affects multiple organs and systems, any professional caring for patients should be aware of it. GD is one of the few hereditary metabolic disorders which can be treated through enzyme substitution therapy with recombinant enzyme. Since early treatment can prevent the development of irreversible physical disabilities, early diagnosis is essential to improve the patient's development. This is why observational epidemiological studies are of help to the doctor in their approach to the diagnosis and treatment of this disease.

We have established in SEOMM a working group on Gaucher disease. To all those associates who are interested in the study of this disease - come and join us!

### Bibliography

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