Persistent bone disease in adult type 1 Gaucher disease despite increasing doses of enzyme replacement therapy

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In Gaucher disease type I (GD, OMIM #230800), deficient activity of the enzyme glucocerebrosidase results in hepatosplenomegaly, cytopenia and skeletal disease.[1] Skeletal disease leads to chronic bone pain and/or severe complications such as pathological fractures, avascular necrosis and bone crises. Enzyme Replacement Therapy (ERT, Cerezyme, Genzyme, MA, USA) reverses many symptoms of the disease with doses ranging between 15 and 120 U/kg/4weeks. Recently, it has been shown that high dose ERT results in a more robust response in Gaucher associated markers, such as chitotriosidase and the bone marrow burden score.[2] Although symptomatic bone disease is usually treated with a relatively high dose (60-120 U/kg/4weeks), bone marrow involvement may persist.[2] Whether it is useful to continue high dose or increase the dose in these cases is currently unknown. We describe one illustrative case and compared GD patients with and without persistent bone disease with respect to disease markers and the effect of dose.

A male patient was diagnosed with GD (genotype N370S/ G202R) at the age of 19 because of persistent splenomegaly during an EBV infection. His first bone crisis occurred at the age of 22 followed by recurrent crises in the femurs, lumbar spine and septic arthritis of his right knee. Splenectomy was performed at age 25 because of gross splenomegaly. ERT was started in 1991 (40 U/kg/4weeks) and normalization of liver volume and modest decrease in chitotriosidase was observed. No new bone complications occurred, although bone pain persisted. Therefore, the dose of ERT was increased stepwise to 120 U/kg/4weeks. After 14 years of ERT, chitotriosidase was still high (8018 nmol/mL/hr) and bone marrow fat fraction low. In 2007 he underwent hip replacement. Pathology of the femoral head showed minimal hematopoietic tissue, large necrotic areas in the center and extensive fields of Gaucher cells (Figure 1).

The files of all adult patients at the Academic Medical Centre receiving ERT for >5 years (N=40), were reviewed. Data on age, sex, splenectomy, severity score index (SSI)[3], weight, hemoglobin, platelet count, liver and spleen volume, QCSI, chitotriosidase, dose and bone complications were collected. Bone response was defined as follows: adequate skeletal response (Group 1): absence of bone complications and chronic bone pain during ERT; treatment failure (Group 2): occurrence of bone complications (avascular necrosis, bone crisis or pathological fractures) or chronic bone pain (requiring analgesics and attributable to GD in the opinion of the physician) during ERT. Chitotriosidase activity was measured as previously described.[4] Liver and spleen volumes were measured by spiral computed axial tomography. To correct for changes in bodyweight, liver ratio was calculated (liver volume/bodyweight (mL/kg)). Bone marrow involvement was assessed using Dixon QCSI of the lumbar spine.[5] Baseline and follow-up QCSI data were available in 15 and 13 patients from group 1 and in one and 6 patients from group 2, respectively. Differences in baseline characteristics were analyzed by the Mann-Whitney or by the χ^2 test. In our experience, chitotriosidase decreases rapidly, with >80% decrease after five years in good responders (unpublished results). Therefore, the time to reach a 80% decrease in chitotriosidase levels and the time to reach a QCSI of more than 23%[6] were analyzed by life table analysis (Kaplan Meier).

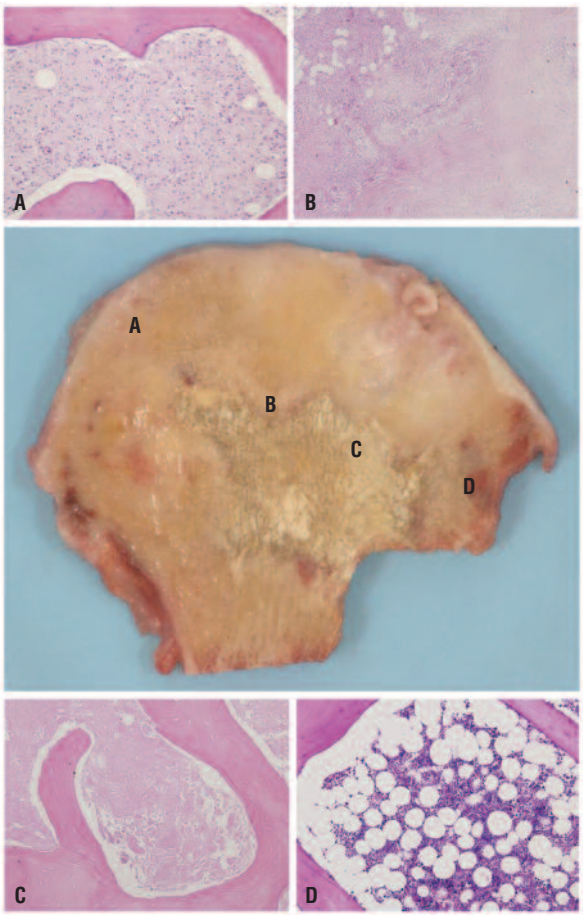

Figure 1. Cross section of left femur head (center). The microscopic pictures above and below highlight (A) the yellowish areas consisting of vital bone and marrow filled with confluent sheets of Gaucher cells (100× magnification), (B) the conspicuous demarcation zone with non-specific chronic inflammation with fibrosis (50×), (C) a central area of necrotic cells surrounded by avital bone devoid of osteocytes (100×), (D) small reddish islands of pre-existent bone marrow with normal hematopoietic tissue (100×).

Differences were determined by the log rank test. At baseline, patients from group 2 had lower bodyweight and more severe disease, as evidenced by a higher SSI and liver ratio, more splenectomies and more pre-ERT bone complications (Table 1).

In Group 1, dose was increased in 10/28 of patients (36%), including all patients with pre-ERT bone complications, primarily because of suboptimal platelet or visceral response. In 3, chitotriosidase and/or fat fractions showed an accelerated improvement after a dose increase (median increase 22.5 U/kg/4 weeks [range 15-105]). In group 2, 10/12 patients (83%, of which 9 patients had pre-ERT bone complications), had a dose increase (median increase 45 U/kg/4 weeks [range 15-105]), two refusing an increase. Chitotriosidase response improved in only 2 patients and fat fraction remained unchanged. After ten years, despite a dose increase to 120 U/kg/4 weeks in 4 patients, absolute QCSI was 14%, 6%, 21% and 15%, compared to a median (range) of 48.5% (25-65%) in group 1. The decrease in chitotriosidase was 48%, 57%, 80% and 52%, compared to a median (range) of 85% (64-88%) in group 1. The time to reach a QCSI of >23% was significantly slower in group 2 (median 132

Table 1. Baseline characteristics (at start of therapy) of patients with (group 2) and without (group 1) severe bone disease after start of ERT.

	Group 1	*Group 2*	*p*
N	28	12	
age	48 (21-68)	51 (37-77)	NS
Sex (male/female)	14/14	9/3	NS
Weight (kg)	74 (50-104)	66 (47-72)	0.026
Splenectomy	6 (21%)	8 (67%)	0.011
Severity Score Index	6 (3-18)	14 (7-19)	<0.0001
Hemoglobin (mmol/L)	7.6 (6.4-9.0)	7.3 (6.5-9.1)	NS
Platelet count (x10^9/L)	77 (41-240)	126 (16-473)	NS
Chitotriosidase (nmol/mL/hr)	35134 (12430-143758)	44973 (29703-151400)	NS
MIP-1β (pg/mL)	199 (72-472)	250 (113-671)	NS
Liver ratio (mL/kg) Spleen volume (mL)	37 (22-93) 1131 (470-4526)	63 (30-130) 1400 (501-4821)	0.014 NS
Patients with pre-ERT bone complications	7 (25%)	10 (83%)	<0.0001
Patients compound heterozygous for N370S	4 (14%)	1 (8%)	NS
Start dose (U/kg/4 weeks)	15 (15-60)	15 (15-50)	NS
Highest dose (U/kg/4 weeks)	30 (15-120)	60 (25-120)	0.007

NS: not significant.

months) versus group 1 (median 24 months, p=0.001). At five years of ERT, all patients from group 1 had reached this goal, compared to 1 patient from group 2. The time to >80% decrease in chitotriosidase was significantly shorter (median 70 months in group 1 *vs.* 172 months in group 2, p=0.008).

We show that a subset of Gaucher type I patients experience ongoing bone disease despite increasing doses of ERT. The selected case illustrates that sanctuary sites of Gaucher cells can remain in the bone marrow. Possibly, the remaining Gaucher cells escape the effects of ERT due to altered vascularization and fibrosis, or sub-populations of Gaucher cells differ in their ability to take up the exogenous enzyme. Indeed, some Gaucher cells may exhibit little immunoreactivity for the mannose receptor.[7]

Twelve out of 40 patients still experienced bone disease despite increasing doses of enzyme. We recently described that these patients have generally higher MIP-1β levels and lower bone marrow fat fractions.[6,8] Assessment of baseline characteristics and response parameters may provide a risk indication for failure of skeletal response, being low body weight, longstanding and severe pre-treatment disease manifestations, (previous bone complications, severe hepatomegaly and splenectomy), as well as slow improvement in QCSI, chitotriosidase and MIP-1β[8] during ERT. In these patients, further dose increases are probably not effective, and dose decrease to maintain adequate visceral control, as well as alternative strategies including the addition of bisphosphonates or substrate reduction, could be explored.

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