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ARTICLE

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Bone marrow response in treated patients with Gaucher disease: evaluation by T1-weighted magnetic resonance images and correlation with reduction in liver and spleen volume

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Abstract *Purpose*. To determine whether T1-weighted magnetic resonance (MR) images can demonstrate response in the marrow of patients with type 1 Gaucher disease treated with enzyme replacement therapy (ERT) and to determine whether a relationship exists between liver and spleen volume reductions and visible marrow changes.
Patients. Forty-two patients with type 1 Gaucher disease were evaluated on at least two occasions. Thirty-two patients received ERT. Of these patients, 15 had a baseline examination prior to the initiation of ERT. The remaining 10 patients did not receive ERT.
Design. T1-weighted and gradient recalled echo (GRE) coronal images of the femurs and hips were obtained. Concurrently, liver and spleen volumes were determined using contiguous breath-hold axial gradient-echo images. T1-weighted images of the hips and femurs were evaluated to determine change or lack of change in the yellow marrow.
Results. Of the 32 patients receiving ERT, 14 (44%) demonstrated increased signal on T1-weighted images suggesting an increase in the amount of yellow marrow. If only the 15 patients with a baseline examination were considered, the response rate to ERT was 67%. Using Student's *t*-test a highly significant correlation ($P<0.005$) was found between marrow response and reduction in liver and spleen volume.
Conclusions. Marrow changes in patients receiving ERT can be detected by T1-weighted images. This response correlated with reductions in visceral volumes ($P<0.0005$).

Keywords Gaucher disease · MRI · Enzyme replacement therapy · Liver · Spleen · Bone marrow

Introduction

Gaucher disease is the most common inherited metabolic disorder of glycolipid metabolism [1]. The genetics of the disorder and the clinical expression of disease have been well covered elsewhere [1, 12]. The non-neuropathic form is termed type 1 and is by far the most common, comprising 95% of cases. Manifestations of this disease can be found in all age groups. The disease stems from a deficiency of the lysosomal enzyme glucocerebroside, acid beta-glucosidase, resulting in the deposition of glucosylceramide within macrophages of the reticuloendothelial system [1, 2]. Clinically this results in a multisystemic disorder involving the hematopoietic [2], respiratory [3, 4], and skeletal systems [5, 6]. The presentation of the disease is varied with frequent involvement of one or two organ systems of varying severity and age of onset.

Imaging abnormalities include hepatosplenomegaly [7], pulmonary changes including pulmonary hypertension, and a complex marrow and bone disorder frequently complicated by the disabling changes of avascular necrosis [5]. Although incompletely understood, skeletal imaging manifestations in patients with Gaucher disease result from several interrelated processes. The gradual

accumulation within the marrow of glucosylceramide-laden macrophages, termed Gaucher cells, causes crowding of the marrow space and replacement of fatty marrow by Gaucher cells [2]. The associated anemia with its hematopoietic stimulus furthers stimulates conversion of yellow to red marrow. Increased osteoclast activity which results in cortical thinning predisposes to pathological fracture [17]. Acute ischemic events, whether a result of marrow hypertension or embolic phenomena, punctuate the more indolent process causing bone crisis, medullary bone infarct and avascular necrosis [6].

Since 1991, treatment has become available in the form of enzyme replacement therapy (ERT) either from the placentally derived enzyme alglucerase (Ceredase) or, more recently, from a recombinant enzyme production method, imiglucerase (Cerezyme) [6, 8, 9]. Reduction in liver and spleen volumes as well as improvement in quality of life is well established with various dosage regimes [10, 11, 12]. Improvement in skeletal disease with ERT as measured by a variety of parameters [2, 6, 13, 14] is thought to lag behind reductions in visceral volumes [6, 13]; however, systematic correlation with skeletal assessment by magnetic resonance (MR) imaging has not been performed.

A variety of methods have been employed to track the skeletal changes with therapy. These methods include plain radiography [5, 6], MR imaging [15–17], and nuclear medicine methods [18, 19]. More quantitative methods have been promoted such as dual-energy X-ray absorptiometry [20], quantitative CT (QCT) [21] and various quantitative MR imaging methods such as those exploiting chemical shift [22] and those relying on assessment of T1 relaxation [23]. Unfortunately, no universally agreed method has been adopted, although the need is clear given the costs of treatment as opposed to the costs of complications. Nonetheless, it is reasonably clear that imaging changes do occur in the marrow with varying rapidity. The nature of these changes is thought to reflect elimination or reduction of the Gaucher cells from the marrow and reduction of anemia, hence conversion of the erythropoietically stimulated red marrow to yellow marrow [22]. It would therefore be expected that the amount of fatty marrow should increase with successful treatment in the Gaucher patient and evidence exists to this effect. The quantitative methods utilizing chemical shift imaging make the assumption of an increase in the proportion of fatty marrow and exploit this feature for the extraction of quantitative data. These quantitative methods are not universally available outside a few large centers, although Gaucher patients are frequently seen elsewhere. Reports of qualitative assessment of marrow changes with ERT using conventional MR imaging methods are of limited patient numbers [14].

This paper seeks first to determine whether bone marrow changes can be detected qualitatively using MR imaging methods in a substantially larger patient group. Secondarily this paper seeks to determine whether a correlation exists between the easily quantifiable liver and spleen volumes and the skeletal changes.

Subjects and methods

A total of 79 patients with type 1 Gaucher disease were examined as part of their clinical evaluation. Of these, 44 were examined on multiple occasions at approximately 12–15 month intervals. Ten patients had prior splenectomy. There were two patients who were skeletally immature and they were ultimately excluded from this analysis since marrow changes in the younger population need to be compared with age-specific standards to allow for normal developmental marrow conversion. Total follow-up period ranged from 13 to 62 months. Of the 42 remaining patients, there were 26 females and 16 males in the study group ranging in age from 16 to 78 years with a mean age of 42 years. Fifteen patients had an initial examination prior to the initiation of ERT alglucerase and imiglucerase (Ceredase and Cerezyme, respectively) (Genzyme Corporation, Cambridge, Mass.), while 17 patients had their first evaluation after receiving ERT for a variable period. Seven patients did not receive ERT but were followed by multiple examinations and three patients began treatment after the last available examination, giving 10 controls and leaving 32 patients who were on treatment and were serially examined. Fifteen patients were treated with high-dose therapy of 60 U/kg every 2 weeks, 12 patients were treated at a medium dose of 30 U/kg every 2 weeks, and five patients were treated at low dose of 7 U/kg weekly. Studies were performed as part of IRB-approved prospective studies of the effect of enzyme replacement therapy in patients with Gaucher disease.

MR protocol

MR imaging was performed on a 1.5-T Signa MR scanner (General Electric, Milwaukee, Wis.). The following imaging protocol was used: a T1-weighted coronal sequence of the femurs (hips to knees) with the following parameters: 650/17 (TR/TE), 48 cm field of view (FOV), 4 mm slice thickness, 0.5 mm interslice spacing, 512×256 matrix, and two signals averaged. Multiplanar gradient-recalled-echo images for T2* contrast were obtained in the coronal plane with the following parameters: 550/15, 20° flip angle, 48 cm FOV, 4 mm slice thickness, 0.5 mm interslice gap, 512×256 matrix, and two signals averaged. Sagittal T1-weighted images of the hips taken with a 20 cm FOV, 256×192 matrix, and a 5 mm slice thickness with a 1 mm skip were obtained specifically for evaluation of avascular necrosis. A vial of cupric sulfate was included in the FOV to prevent rescaling in the event that subsequent regions of interest were to be compared.

At the time of each skeletal examination, the liver and spleen volumes were also obtained using a protocol for a magnetization prepared RF spoiled gradient-echo sequence: 600 ms TI, 9.8/2.5 TR/TE, 30° flip angle, 30–38 cm FOV, 10 mm slice thickness, no interslice gap, 256×128 matrix, and two signals averaged. Volumes of the liver and spleen were calculated with a method much like that of Rosenthal et al. [15]. The areas were manually outlined and integrated with computer assistance. The areas of all slices were summed (multiplied by 10 mm slice thickness and divided by 1000). The volumes were expressed in cubic centimeters.

The MR examinations of all included patients were evaluated for changes over the greatest follow-up interval available by two musculoskeletal radiologists experienced in the interpretation of MR examinations of Gaucher patients and masked to treatment information. Although changes were, at times, detected in shorter

intervals, none was less than 13 months. Since the only decision called for by the readers was "responding" or "non-responding" we felt justified in this approach. T1-weighted images were evaluated for changes in overall signal, with subcutaneous fat used as an internal standard. Interval changes were typed with only two choices permitted: non-responding (no change in T1 signal over the interval) and responding (homogeneous interval increase in T1 signal) or patchy increase in T1 signal with non-responding lesions appearing more conspicuous. The marrow responses of these groups were correlated with reductions in liver and spleen volume by Student's *t*-test.

Results

Table 1 summarizes the results of this analysis. There were 42 patients with serial examinations of whom 32 were on ERT. A total of 27 patients (64%) were classified as non-responding. Of these 27 patients, nine were either not on therapy or began ERT after the last examination; therefore, 18 of 32 (56%) treated patients were non-responding. A single patient with non-responding marrow changes appeared to have developed avascular necrosis over the study interval. This patient's marrow appeared unchanged in spite of ERT. Fourteen patients (44%) of those on ERT showed definite increases in T1 marrow signal presumed to represent fatty marrow (Figs. 1, 2, 3). A subgroup of five patients (36%) had heterogeneous increases in T1 so that non-responding zones stood out with greater conspicuity. In some cases, the pre-existent lesions were not visible (Fig. 1) on pretreatment scans. Whether visible on pretreatment T1-

Table 1 Patient demographics (*AVN* avascular necrosis)

Age/Sex	T1 response	Examination interval (months)	Liver change (%)	Spleen change (%)	Enzyme replacement therapy
17F	–	55	20%	Splenectomy	High
52F	–	44	–33%	Splenectomy	High
52F	–	39	–28%	Splenectomy	High
57F	–	15	–9%	Splenectomy	High
59M	–	32	–4%	Splenectomy	High
67F	–	22	8%	Splenectomy	None
70F	–	45	–7%	Splenectomy	None
78M	–	39	–15%	Splenectomy	Low
47F	–	56	–15%	–71%	Medium[a]
53M	–	12	–24%	–66%	High[a]
67F	–	31	–13%	–57%	High[a]
32F	–	33	–19%	–35%	Medium
60F	–	49	–13%	–33%	High[a]
28F	–	62	12%	–33%	None
42M	–	36	20%	–26%	Medium[a]
28F	–	47	36%	–24%	Medium
43F	–	14	–6%	–16%	Low
46M	–	20	–14%	–16%	Medium
35F	–	38	15%	–12%	High
66M	–	14	10%	–10%	None
43M	–	44	23%	22%	None
19M	–	25	58%	23%	None
34F	–	39	12%	24%	None
16M	–	35	11%	28%	None
29M	–	13	8%	30%	Low
34F	–	33	20%	34%	None
70M	–	45	101%	87%	Medium
51M	– (AVN)	25	–13%	–4%	High
34F	+	35	–32%	Splenectomy	Medium[a]
26M	+	29	–53%	Splenectomy	High
56F	+	55	–60%	–72%	High[a]
38F	+	30	–23%	–65%	Medium[a]
20F	+	13	–24%	–63%	High[a]
63F	+	55	–28%	–61%	Low[a]
56F	+	48	–26%	–60%	Medium[a]
53F	+	29	–16%	–57%	Medium[a]
55M	+	49	–25%	–50%	High[a]
48M	+	36	–10%	–47%	Medium[a]
25F	+	23	–11%	–47%	Medium
35F	+	23	–39%	–31%	Low[a]
47M	+	13	–5%	–31%	High[a]
44F	+	35	59%	7%	None

[a] Indicates pretreatment baseline studies

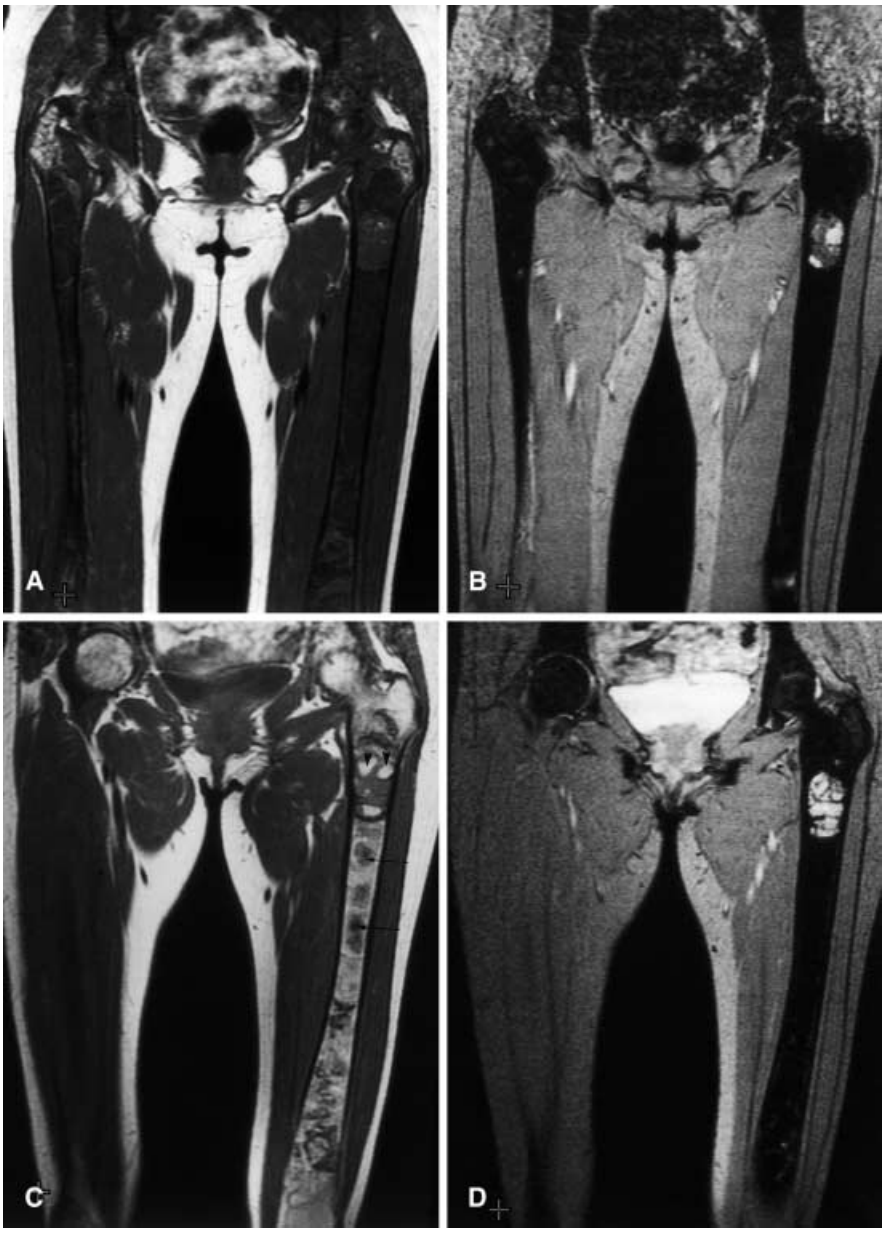

Fig. 1A–D A 63-year-old woman beginning enzyme replacement therapy for Gaucher disease in February 1994. **A** T1-weighted coronal images of the femurs, TR/TE 650/17, obtained in February 1994. The signal in the femoral shafts is notably low, particularly when compared with the subcutaneous fat. A single large lesion can be seen in the proximal shaft. **B** Gradient recalled echo image, TR/TE/flip 550/15/20, obtained in February 1994. There is a bright signal lesion in the subtrochanteric femur corresponding to that seen in **A**. The patient's femurs exhibited increased T2* signal, decreased T1 signal, and absence of avascular necrosis. **C** Follow-up T1-weighted coronal images, TR/TE 650/17, obtained in September 1996. There has been an obvious increase in marrow fat making previously invisible small lesions in the femoral diaphysis (*arrows*) now visible. The larger, more proximal lesion can be seen more sharply and material of lipid resonance (*arrowheads*) has been deposited within the lesion. **D** Follow-up gradient recall coronal images, TR/TE/flip 550/15/20, obtained in September 1996. There is no apparent change in the marrow appearance when compared with the earlier study

weighted images or not, focal lesions were generally detectable as high signal zones on the GRE sequence component of the study (Figs. 1b, 1d, 2b, 2d), helping to distinguish them from lesions that had developed in the treatment interval. No significant T2* changes were detected on serial GRE sequences over the treatment interval. All patients exhibiting increased T1 signal had been on one of the three treatment regimens with a single exception who had not been on ERT. If only patients with a pretreatment baseline studies are considered, only four of 16 (25%) failed to respond while 12 of 16 (75%) were in the responding group. There were two patients who were placed on therapy with normal pretreatment marrow images. This affected the results since no change could be expected and none was seen. If these two patients are excluded from the pretreatment baseline studies, two of 14 (14%) patients failed to respond while the remaining 12 of 14 (86%) responded to ERT.

The percent change in liver and spleen volumes was correlated with T1 changes (Figs. 4, 5) and analyzed by a Student's *t*-test. The mean change in liver volume was 6% for the non-responding group, while the mean reduction was –20% for the patients with responding marrow (P=0.005). In the case of the spleen, the mean volume reduction was –4% for non-responder, but –50% for the responding group (P=0.00038).

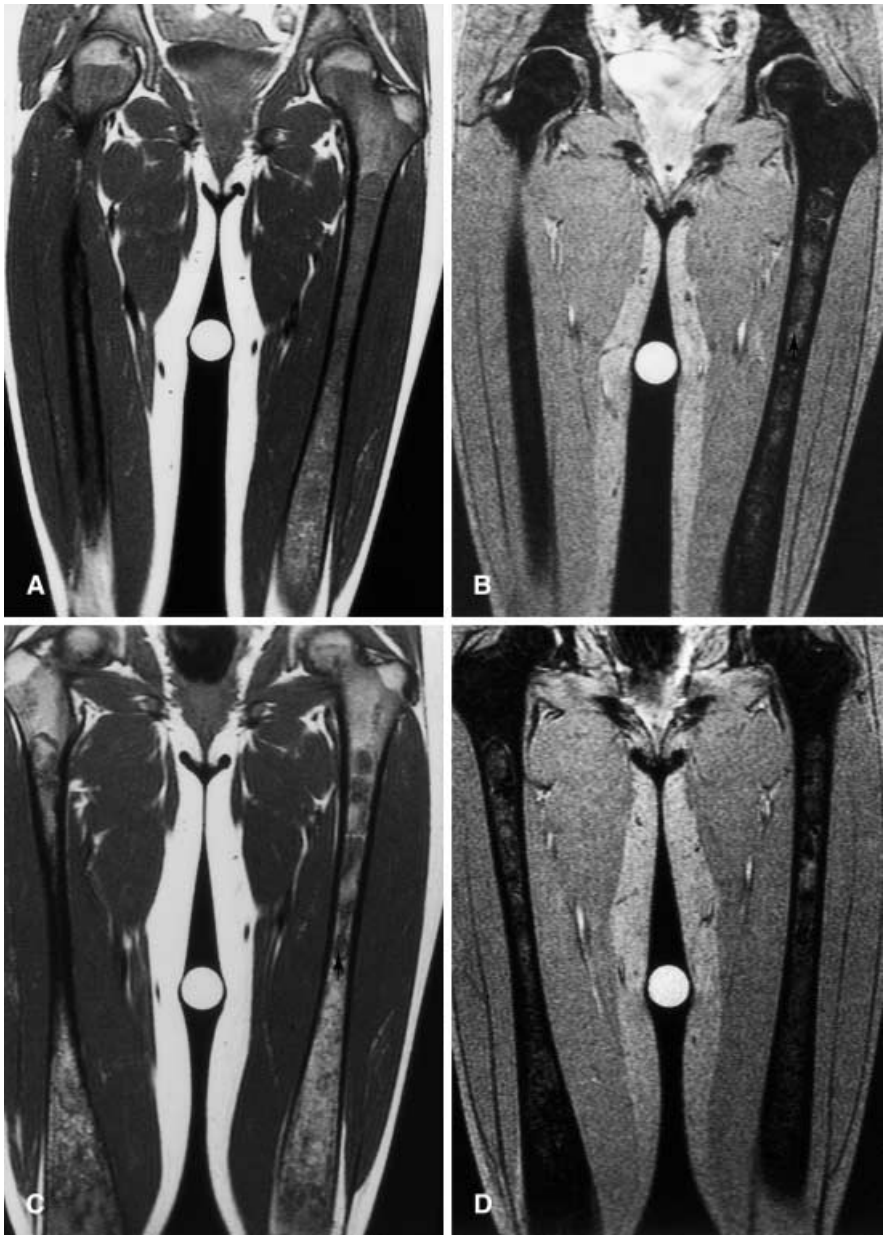

Fig. 2A–D A 23-year old woman placed on enzyme replacement therapy in October 1997. **A** T1-weighted coronal images, TR/TE 650/17, obtained in October 1997 immediately before the initiation of enzyme replacement therapy. The marrow fat is diffusely reduced in signal. Focal diaphyseal lesions are not distinct. **B** Gradient recalled echo (GRE) image, TR/TE/flip 550/15/20, obtained in October 1997 prior to enzyme replacement therapy. Abnormal high signal is present in the diaphysis (*arrow*). **C** Follow-up T1-weighted coronal images, TR/TE 50/17, obtained in November 1998. There is increased T1 signal noted generally but focal diaphyseal lesions are now clearly seen (*arrow*). These lesions correspond to those seen on the prior GRE examination (**B**). **D** Follow-up GRE images, TR/TE/flip 550/15/20, obtained in November 1998. Note that there is no apparent change when compared with **B**. The lesions which have become more obvious on T1-weighted images were pre existent and are unchanged with treatment

The average follow-up period for treated patients with non-responding marrow was 35 months (range 14–38 months) and 33.6 months (range 13–54 months) for the responding group. The mean age of patients exhibiting non-responding marrow was 58.7 years and the mean age for those with responding marrow was 50 years. The shortest interval over which marrow changes were detected was 13 months. There were 10 patients who had prior splenectomy. Of this group only two (20%) showed increased marrow fat (responding group) with treatment. The marrow response in patients with splenectomy was compared with the response in patients with intact spleens using a chi-square test. The *P* value of 0.55 was considered not significant.

Discussion

Gaucher disease results in the deposition of Gaucher cells in the marrow causing a reduction in lipid-containing marrow in affected patients. Treatment has been shown to result in increased marrow fat [14] detectable with T1-weighted MR sequences. Our data support this conclusion in a substantially larger group: 42 patients in this study as opposed to the three patients reported by Allison et al. [14]. We made the decision to exclude patients who were younger than 14 years of age since there is a developmental conversion from red to yellow marrow in children which could be mistaken for changes caused by

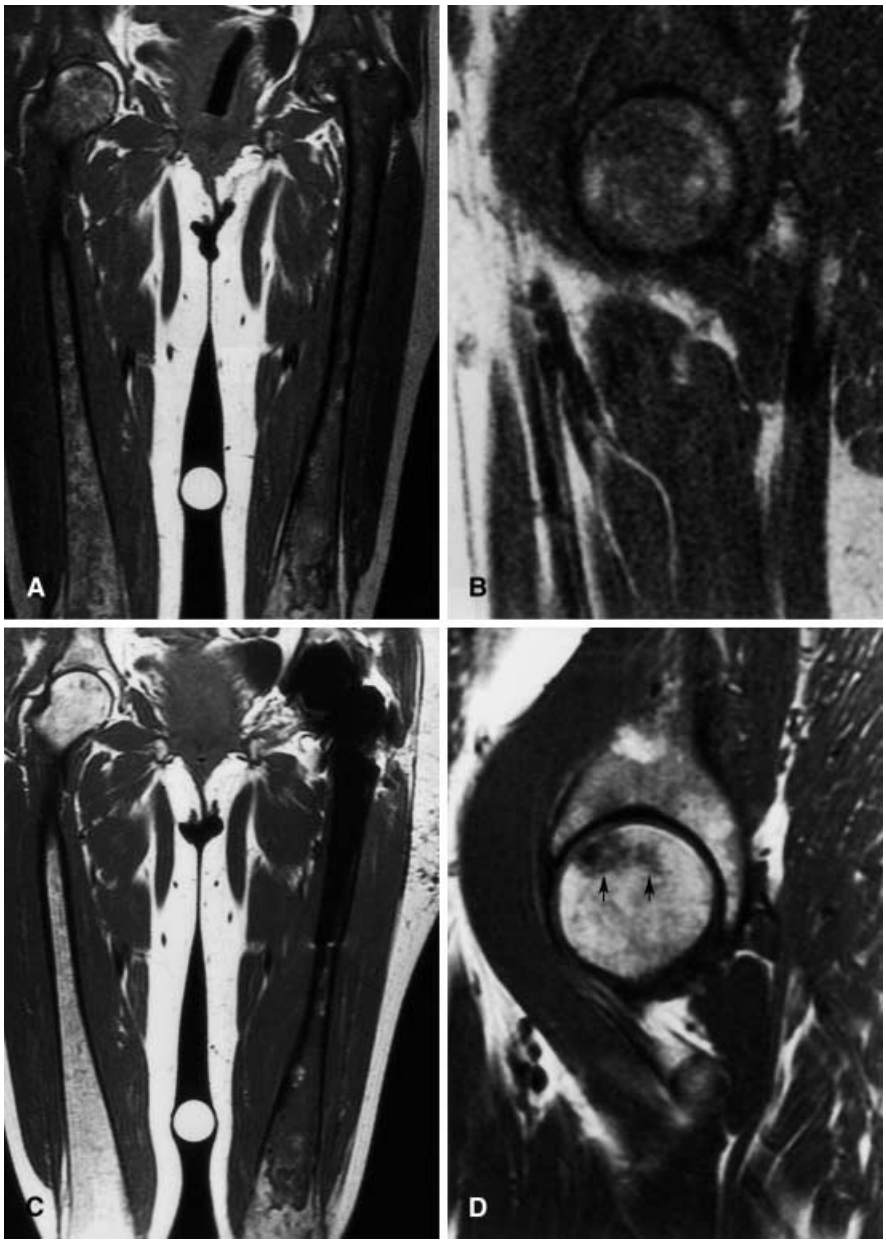

Fig. 3A–D A 56-yearold woman with type 1 Gaucher disease and severe right hip pain. The patient started on enzyme replacement therapy in August 1994 shortly after images in **A** and **B** were obtained. **A** T1-weighted coronal image, TR/TE 650/17, obtained in August 1994 prior to the initiation of enzyme replacement therapy showing low marrow signal throughout the visualized marrow. There is collapse of the left hip as a complication of avascular necrosis. **B** T1-weighted sagittal image of the right hip obtained prior to the initiation of enzyme replacement therapy: TR/TE 650/16, FOV 20, matrix 256×192, 2 NEX. Note the very low signal in the marrow relative to the subcutaneous fat. Focal lesions are difficult to identify. **C** T1-weighted coronal images, TR/TE 650/17, obtained in March 1998. There has been a marked increase in signal from the marrow. The patient has also had a total hip arthroplasty in the interval. **D** T1-weighted sagittal image of the right hip, TR/TE 650/17. Because of the increased background signal from the marrow fat a zone of avascular necrosis can now be seen (*arrows*). In retrospect this lesion can be seen in **B**

ERT. Indeed, this type of analysis is probably unsuitable in the evaluation of children without well-established age-matched controls.

Earlier data [7] have suggested a relationship between liver and spleen volume and marrow abnormalities. The current data indicate that treated patients who show a marrow response also have a parallel reduction in hepatosplenomegaly that can be measured. The data also suggest two statistically different groups of treated patients: those who respond with both marrow improvement and visceral volume reduction, and those whose marrow fails to respond and whose liver and spleen volumes remain largely unchanged. There may be some as yet unknown differences between these patients biologically. Clearly, among the possibilities for the failure of response might be inadequate dosage; however, because there were numerous dosage changes we felt ourselves unable to examine the issue of optimal or appropriate dosage. This remains an important area for investigation and our MR methods for evaluation may be suitable for such a study. Although the genotypes are known for some patients, they are not known for all. Future correlation with genotypes may be interesting. Alternatively, lack of marrow response with visceral volume reductions might suggest that more prolonged follow-up of the bones is appropriate or that volume measurements are less prone to error

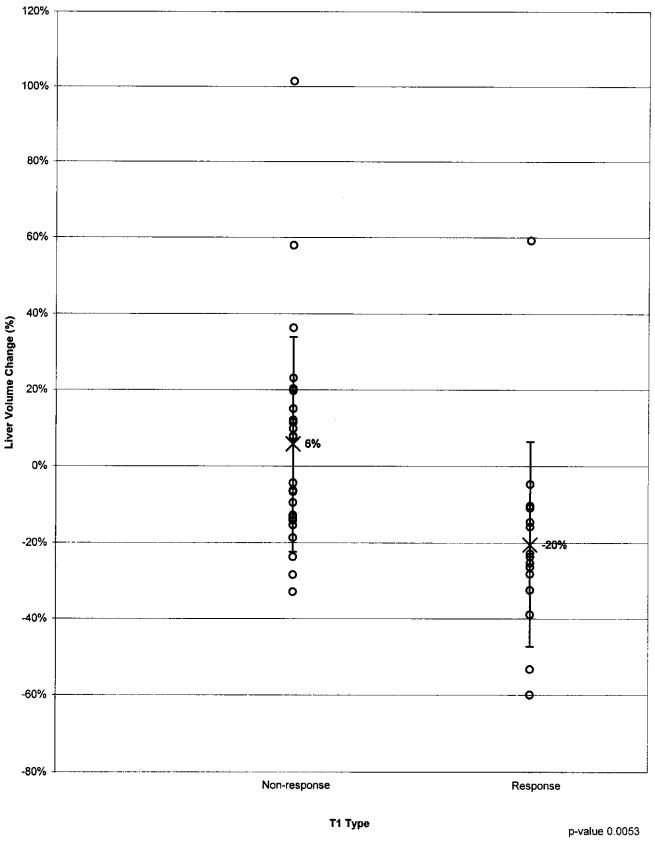

Fig. 4 Plot of T1 marrow change types against liver volume changes. Mean volumes are shown numerically

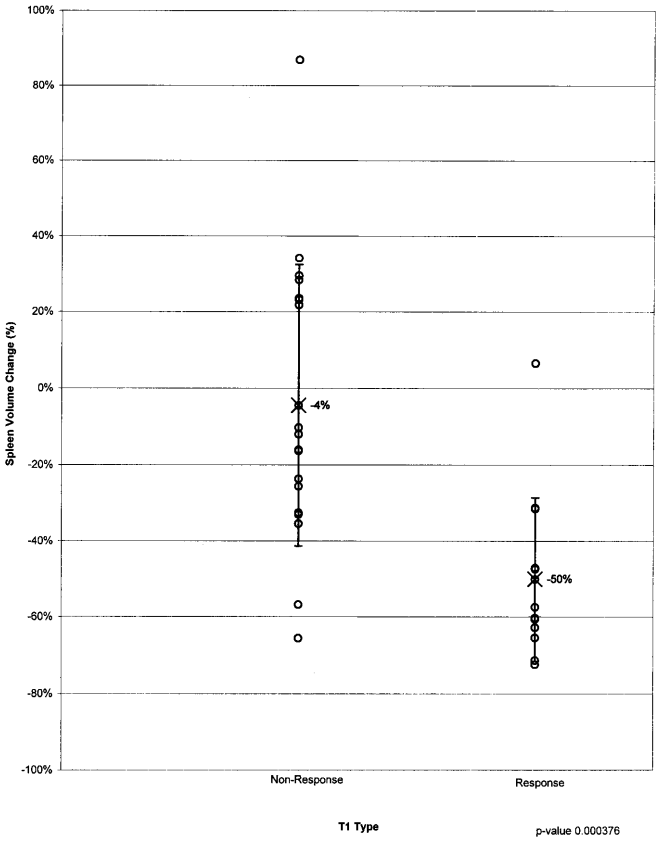

Fig. 5 Plot of T1 marrow change types against spleen volume changes. Mean volumes are shown numerically. There are fewer data points than in Fig. 4 because of the patients who had splenectomy

than the admittedly more subjective marrow classification used here.

The reduced marrow response in patients who had prior splenectomy may bear notice. Although this is a small subset of patients, the 25% response is substantially less than the overall response rate of 44% among all patients receiving ERT. Indeed if we look at only non-splenectomized patients the response rate becomes 12 of 24 (50%). One can speculate that removal of the spleen eliminates a reservoir for accumulation of glucosylceramide and that without this organ the load deposited in the bone marrow may be greater, leading to more irreversible changes.

The finding of apparent development or worsening of focal lesions in a subset of responding patients was of interest particularly since there are important implications. First, it is possible that the paradoxical appearance of such false lesions might be misinterpreted as the development of a new lesion if only T1-weighted images are used. This group of patients, however, had T2* changes suggesting complicated, irreversible lesions probably resulting from bone infarct. These lesions are not reversible but were probably isointense to surrounding marrow on the initial T1-weighted images, only becoming visible as low signal lesions when the surrounding viable marrow increased in fat content. It was of interest to note that the GRE images were essentially unchanged in responding as well as non-responding patients. Recognition of this effect is important since it avoids a potential pitfall in interpretation. Misinterpretation can be avoided by careful scrutiny of the GRE images. Second, the low conspicuity of these lesions in the untreated patient makes it particularly difficult to detect avascular necrosis (Fig. 3). The threshold for suspicion therefore needs to be lowered in the evaluation of T1-weighted images from patients with low background T1 signal.

Patients were treated by different treatment regimens. There were some changes in dosage during the course of the study that complicated the analysis and we feel our data to be insufficient to arrive at any conclusion. Responding and non-responding marrow was found in all treatment groups. The single patient who developed avascular necrosis was on high-dose therapy. There are two interesting speculations in this case: that avascular necrosis occurred in spite of the therapy or already existed but was not appreciated because the lesion was at that time isointense to fat-deficient marrow. The issue of dose remains unresolved due to the chang-

es in regimen and may have been inappropriately low for this patient.

An interesting question is how early can marrow changes be expected to be seen. In our group of patients, the earliest changes were noted in one patient at 14 months and in two patients at 13 months. These were the first follow-up studies after the beginning of ERT. This finding suggests that in some patients increase in fatty marrow may be seen as early as 13 months, paralleling the visceral volume changes. There were no data obtained at a shorter interval and it remains possible that increases in fatty marrow may occur earlier. Neither patient age nor sex appears to be useful in separating patients whose marrow will respond from patients whose marrow appears not to.

Including patients who did not have baseline examinations biased our data. If these patients are excluded, 75% of treated patients can be seen to respond. In addition, there were two patients with initially normal-appearing marrow in whom response by this measure could not be expected. If we exclude these patients, the positive response to ERT is 12 of 14 (86%).

Among the objections that may be raised to this study is the lack of quantitative marrow data. Although we are now acquiring quantitative H1 spectroscopic data these techniques were not available in the majority of earlier comparison examinations. We attempted region of interest intensity measurements but lacked confidence in the reliability of these measurements. We were therefore left with a visual assessment alone; however, the qualitative changes were compelling. We look forward to the analysis of H1 spectroscopic data when comparisons become available.

In conclusion, our data indicate that changes in the bone marrow of patients with Gaucher disease treated with ERT can be detected on T1-weighted images. In addition, the group of patients with marrow judged to respond had significantly greater reduction of the liver and spleen volumes than the non-responding group. A high percentage of patients with non-responding marrow had prior splenectomy (80%). The presence of a subgroup with increasing conspicuity of lesions suggests two cautions: first, the threshold for detection of lesions in untreated patients should be lowered and second, most of these lesions should be recognized as pre-existent. Apparent development or worsening of focal lesions can be distinguished from true interval lesions by their presence on GRE sequences. Although quantification of marrow changes following enzyme therapy remains a desirable goal, measurement of visceral volumes appears to be an appropriate alternative.

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References

1. Beutler E, Gaucher's disease. N Engl J Med 1991; 325:1354–1360
2. Rosenthal DI, Doppelt SH, Mankin HJ, et al. Enzyme replacement therapy for Gaucher disease: skeletal responses to macrophage-targeted glucocerebrosidase. Pediatrics 1995; 96:629–637
3. Yassa NA, Wilcox AG. High-resolution CT pulmonary findings in adults with Gaucher's disease. Clin Imaging 1998; 22:339–342
4. Aydin K, Karabulut N, Demirkazik F, Arat A. Pulmonary involvement in adult Gaucher's disease: high resolution CT appearance. Br J Radiol 1997; 70:93–95
5. Stowens DW, Teitelbaum SL, Kahn AJ, Barranger JA. Skeletal complications of Gaucher disease. Medicine 1985; 65:310–322
6. Hermann G, Pastores GM, Abdelwahab IF, Lorerboym AM. Gaucher disease: assessment of skeletal involvement and therapeutic responses to enzyme replacement. Skeletal Radiol 1997; 26:687–697
7. Terk MR, Esplin J, Lee K, Magre G, Colletti PM. MR imaging of patients with type 1 Gaucher's disease: relationship between bone and visceral changes. AJR 1995; 165:599–604
8. Barton RO, Furbish FS, Murray GJ, Garfield M, Brady RO. Therapeutic response to intravenous infusions of glucocerebrosidase in a patient with Gaucher's disease. Proc Natl Acad Sci USA 1990; 87:1913–1916
9. Furbish FS, Steer CJ, Kreet NL, Barranger JA. Uptake and distribution of placental glucocerebrosidase in rat hepatic cells and effects of sequential deglycosylation. Biochim Biophys Acta. 1981; 673:425–434
10. Elstein D, Hadas-Halpern I, Itzchaki M, Lahad A, Abrahamov A, Zimran A. Effect of low-dose enzyme replacement therapy on bones in Gaucher disease patients with severe skeletal involvement. Blood Cells Mol Dis 1996; 22:104–111
11. Brady RO, Barranger JA. Glucosylceramide lipidosis: Gaucher disease. In: Stansbury JB, Wyngaarden JB, Frederickson DS, Goldstein JL, Brown MS, eds. The metabolic case basis of inherited disease. New York: McGraw-Hill, 1983:842–856
12. Damiano AM, Pastores GM, Ware JE. The health-related quality of life of adults with Gaucher's disease receiving enzyme replacement therapy: results from a retrospective study. Qual Life Res 1998; 7:373–386
13. Grabowski GA, Leslie N, Wenstrup R. Enzyme therapy for Gaucher disease: the first 5 years. Blood Rev 1998; 12:115–133
14. Allison JW, James CA, Arnold GL, Stine KC, Becton DL, Bell JM. Reconversion of bone marrow in Gaucher disease treated with therapy documented by MR. Pediatr Radiol 1998; 28:237–240

15. Rosenthal DI, Barton NW, McKusick KA, et al. Quantitative imaging of Gaucher disease. Radiology 1992; 185:841–845
16. Hermann G, Shapiro RS, Abdelwahab F, Grabowski G. MR imaging in adults with Gaucher disease type I: evaluation of marrow involvement and disease activity. Skeletal Radiol 1993; 22:247–251
17. Rosenthal DI, Scott JA, Barranger J, et al. Evaluation of Gaucher disease using magnetic resonance imaging. J Bone Joint Surg Am 1986; 68:802–807
18. Lorberboym M, Vallabhajosula S, Lipzyc H, Pastores G. Scintigraphic evaluation of Tc-99m-low-density lipoprotein (LDL) distribution in patients with Gaucher disease. Clin Genet 1997; 52:7–11
19. Katz K, Mechlis-Frish S, Cohen IJ, Horev G, Zaizov R, Lubin E. Bone scans in the diagnosis of bone crisis in patients who have Gaucher disease. J Bone Joint Surg Am 1991; 73:513–517
20. Pastores GM, Wallenstein S, Desnick RJ, Luckey MM. Bone density in type 1 Gaucher disease. J Bone Miner Res 1996; 11:1801–1807
21. Rosenthal DI, Mayo-Smith W, Goodsitt MM, Doppelt S, Mankin HJ. Bone and bone marrow changes in Gaucher disease: evaluation with quantitative CT . Radiology 1989; 170:143–146
22. Johnson LA, Hoppel BE, Gerard EL, et al. Quantitative chemical shift imaging of vertebral bone marrow in patients with Gaucher disease. Radiology 1992; 182:451–455
23. Magnaldi S, Longo R, Ukmar M, Zanatta M, Bottega M, Sottocasa GL. Bone marrow relaxation times in Gaucher disease before and after enzyme replacement therapy. Eur Radiol 1997; 7:486–491