Clinical applications of Dixon chemical shift MR imaging: Morbus Gaucher, Morbus Hansen

Maas, M.

Publication date
2002

CHAPTER 5

Dixon quantitative chemical shift imaging is a sensitive tool for the evaluation of bone marrow responses to individualized doses of enzyme supplementation therapy in type 1 Gaucher disease

Carla Hollak [1], Mario Maas [2], Erik Akkerman [2], Ard den Heeten [2], Hans Aerts [3]

Dept. of Hematology[1], Radiology[2] and Biochemistry[1], Academic Medical Center, Amsterdam, The Netherlands.

Blood Cells Mol Dis 2001; 27(6):1005-1012

ABSTRACT

Type 1 Gaucher disease can be effectively treated with enzyme supplementation therapy. Bone disease is a debilitating feature of the disorder and results from infiltration of the bone marrow by Gaucher cells. The effect of treatment on bone marrow infiltration is difficult to measure, necessitating the development of sensitive techniques to allow adequate dosing. Dixon quantitative chemical shift imaging (Dixon QCSI) is a MRI technique to measure displacement of fatty marrow by Gaucher cells. Low bone marrow fat-fractions have been found in Gaucher disease. We studied the effect of individualized low doses of enzyme therapy on the fat-fractions of the lumbar spine in 12 adult Gaucher disease patients before and during treatment and in 9 untreated Gaucher controls. Fat-fractions were decreased in 9/12 patients (median 0.20, range 0.08-0.40) and equally low in the untreated Gaucher controls compared to age matched healthy volunteers (normal values 0.27-0.43, $p < 0.01$). During treatment, fat-fractions increased significantly already after 1 year in 11/12 patients (P=0.007). After 4 to 5 years, fat-fractions normalized in 11/12 patients. Fat-fractions remained low in the untreated Gaucher controls ($p = 0.5$ and 0.6 at 1 and 2 years, respectively). Six of 11 patients had a dose increase, which did not clearly affect fat-fractions.

Dixon QCSI is a sensitive tool for the measurement of the respons of bone marrow to enzyme therapy.

INTRODUCTION

Gaucher disease is the most frequently encountered lysosomal storage disorder in man. Deficiency of the lysosomal enzyme glucocerebrosidase (glucosylceramidase, EC 3.2.1.45) leads to accumulation of glucocerebroside in macrophages [1]. The clinical picture of type 1 disease encompasses hepatosplenomegaly, cytopenia, and bone involvement. Bone disease is one of the most debilitating features of type 1 Gaucher disease, including atypical bone pain, osteonecrosis, pathological fractures, and bone crises [1,2]. Enzyme supplementation therapy, using either placentally derived or recombinant glucocerebrosidase (alglucerase or imiglucerase, respectively, manufactured by Genzyme Co., MA) has proven to effectively reverse the clinical manifestations of Gaucher disease. Improvement in cytopenia and reduction of organomegaly belong to the early effects of treatment, usually being apparent after 3 to 6 months [3-5]. Monitoring of these disease manifestations is relatively easy by the application of routine blood tests and widely available modalities such as ultrasound, CT scanning or MRI, for organ volume determinations. Bone disease responds slower and is more difficult to measure. Several imaging techniques are being applied for the assessment of the severity of bone and bone marrow abnormalities. Plain radiographs and quantitative CT scanning for measurement of cortical thickness, densitometry, MRI and fat-fraction determination by Dixon quantitative chemical shift imaging (Dixon QCSI) have been used [3,6-9]. So far, changes in bone structure in respons to alglucerase treatment became apparent after years of treatment [7-9]. For the accurate application and interpretation of these different imaging techniques it is essential to divide bone disease into two different parts as has been done earlier by Rosenthal: bone structure and bone marrow infiltration. It is very likely that these two parts are related to each other: it is hypothesized that bone becomes affected because of progressive infiltration of the bone marrow with foci of Gaucher cells, possibly in combination with a toxic process around these foci [10]. This difference is increasingly important from the perspective of treatment respons assessment. Bone marrow infiltration may be rapidly reduced upon treatment, while structural changes, such as Erlenmeyer flask deformities and cortical thickness may remain unchanged for a long time. For the evaluation of the efficacy of different dosing regimens, early detection of

Gaucher cell clearance from the bone marrow is mandatory to allow dose adjustments in cases of unsatisfactory responses. Therefore, the availability of imaging techniques that focus on the extent of bone marrow infiltration are essential. Dixon QCSI is considered as a sensitive tool for measuring the degree of Gaucher cell infiltration by the decrease in fat-(triglyceride) fraction in the marrow as the result of Gaucher cell infiltration [11]. It has been shown that the triglyceride content of the bone marrow may increase during alglucerase treatment [7].
The aim of the present study is to detect early changes in the bone marrow of adult type 1 Gaucher disease patients by Dixon QCSI measurements during treatment with individualized doses of alglucerase or imiglucerase [9] in relation to overall respons.

METHODS

Patients

All patients that entered the individualized dosing study after July 1993 and completed at least 4 years of enzyme therapy were included in this study. The population consisted of 12 adult type 1 Gaucher disease patients (3 females, 9 males) of whom three were splenectomized (Table 1). A diagnosis of Gaucher disease was confirmed by decreased activity of glucocerebrosidase in leukocytes and genotyping [12,13]. Enzyme therapy was initiated according to the earlier described protocol [9]. In brief, patients are treated during the first 6 months with low doses of enzyme (alglucerase or imiglucerase 1.15 U/kg three times a week) and subsequently evaluated for treatment efficacy every 6 months thereafter. According to defined criteria based on reductions in organomegaly and improvement in cytopenia, the dose is doubled, maintained or halved to allow individualized dosing. In addition, occurrence of bone complications during treatment is an independent reason for a dose increase. Blood counts were taken every 6 months. Organ volume measurements were performed using spiral CT scanning initially every 6 months and yearly after 3 years of treatment. Dixon QCSI measurements were obtained before the initiation of enzyme supplementation therapy and every year thereafter.

Table 1. Characteristics of Gaucher disease patients before treatment with enzyme therapy (treatment group) and untreated Gaucher controls

Treatment group						Untreated Gaucher controls					
No.	sex	age (yrs)	splenic status	bone compl	SSI	No.	sex	age (yrs)	splenic status	bone compl	SSI
1	M	48	Intact	No	9	1	M	47	Intact	No	4
2	F	53	Intact	No	8	2	F	43	Intact	No	4
3	M	38	Intact	No	7	3	F	55	Intact	No	6
4	M	53	Intact	No	5	4	M	19	Intact	No	6
5	M	43	Intact	No	5	5	F	39	Intact	No	4
6	M	51	Intact	No	5	6	F	43	Intact	No	2
7	M	48	Intact	No	5	7	F	35	Intact	No	4
8	M	37	Sx	Yes	17	8	M	34	Sx	No	6
9	M	57	Sx	Yes	16	9	F	30	Sx	No	11
10	F	39	Sx	Yes	18						
11	F	38	Intact	No	4						
12	M	29	Intact	No	8						

Controls

Nine adult type 1 Gaucher disease patients that did not need or want treatment and were followed for at least 12 months served as controls (untreated Gaucher controls). This population was less severely affected than the treated patient group. Organ volumes, hematology and bone marrow fat-fractions were measured every year in these untreated patients.

Dixon-QCSI fat-fraction acquisition

In-phase and opposed-phase proton density weighted spin echo sequences were performed: TR 2500 ms, TE 22.3 ms, slice thickness 4 mm, matrix 256x256, NEX 1, FOV 350x350 mm^2, acquisition time 21 min 20 s. The paracoronal measurement acquisition slices were positioned on a mid-sagittal localizer image, passing through the middle of the posterior parts of L3, L4, and L5.

Post-processing and data analysis were performed on a Sun Sparc 20-51 workstation (Sun Microsystems, Mountain View, CA), using a previously described algorithm [14,15].
To obtain one fat-fraction value for each vertebra, we averaged the pixel values in a region of interest (ROI). The mean bone marrow fat-fraction was calculated from measurements in three separate lumbar vertebrae (L3-L5).
Standardization and reproducibility of the Dixon QCSI protocol was performed by measurements in 16 healthy volunteers (16).

Statistics
Results are given as median and range. Differences between data from patients and controls were tested by Mann-Whitney test. Differences between data obtained before and during enzyme supplementation therapy were tested by the Wilcoxon signed-rank test. A p value of <0.05 respresented a significant difference.

RESULTS

Patients
Of the 12 patients, 3 (all splenectomized) had suffered from avascular necrosis, pathological fractures and/or bone crises and 9 had not (Table 1). Patient 9 had experienced a bone crisis at the time of initial examination, located in the lumbar spine and pelvis, treated with analgesic drugs. During treatment with alglucerase, he developed a collapse of vertebral bodies L3 and L4.
No further bone complications occurred during treatment, although patient 10 experienced recurrent episodes of atypical bone pain, which led to a dose increase.
Eleven patients were initially treated with alglucerase, 1.15 U/kg three times a week and one patient (No.1) was treated with 30 U/kg every 2 weeks, because of inability to perform home treatment. Respons to treatment after 6 months according to the defined criteria was classified as moderate in 6 and insufficient in 4 (patients 4,6,10, and 12). During 4 years of treatment, doses were adjusted according to further clinical responses.

Table 2 shows the results of bone marrow fat-fraction determinations by Dixon QCSI, hemoglobin levels, platelet counts and organ volumes in relation to dose at the start of treatment and after 4 years. In patients 2 and 3 the examinations at 5 years were used, because no evaluation was performed after 4 years of treatment.

Table 2. Bone marrow fat-fractions (F), hematology, organ volumes, and dosing regimens before and after 4 to 5 years of treatment

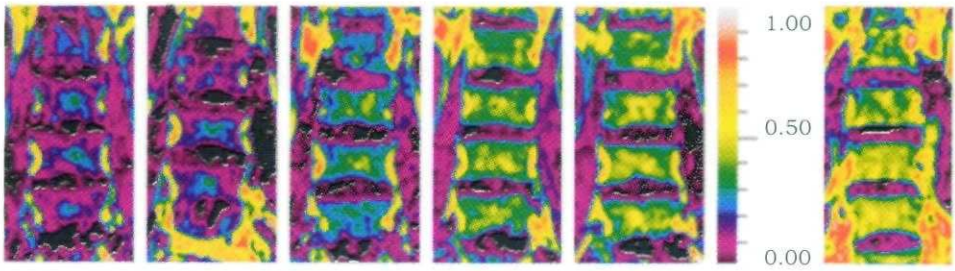
	F (%)		Hb level (g/dl)		platelet count (x 10^9/L)		spleen volume (ml)		liver volume (ml)		dose (U/mo)	
No.	start	4 yrs	start	4 yrs	start	4 yrs	start	4 yrs	start	4 yrs	start	4 yrs
1	18	47	15.0	15.8	118	164	855	362	2269	1557	60	30
2*	22	41	10.9	11.8	48	129	1042	422	3139	2311	15	15
3*	10	18	14.6	14.6	122	156	1400	549	3695	1997	15	15
4	23	38	11.2	13.0	53	69	3118	2629	3334	2418	15	60
5	29	47	15.0	14.7	110	169	574	326	1830	1656	15	15
6	18	35	11.7	13.0	71	126	2002	823	3678	2808	15	30
7	40	50	13.8	14.4	45	145	885	438	2014	1608	15	15
8	11	28	10.1	12.2	129	320			3691	2566	15	30
9	34	42	9.3	12.5	726	457			2393	1645	15	30
10	11	30	15.8	14.4	189	286			4139	1550	15	120
11	22	48	13.1	14.6	103	246	535	256	1797	1516	15	15
12	8	28	13.4	14.9	59	58	4379	1751	3426	2445	15	40

* in pts. 2 and 3, the 5-year examination was used

Bone marrow fat-fractions

Before treatment, fat-fractions were decreased in 9/12 patients (median 0.20, range 0.08-0.40) compared to healthy volunteers with the same age and sex distribution (normal values 0.27-0.43, $p < 0.01$) [16]. The values of the initial measurements in the Gaucher patients who were going to be treated were not significantly different from the values in the untreated Gaucher controls: 5/9 had decreased fat-fractions (median 0.22, range 0.10-0.36; $p = 0.7$).

Figure 1 shows the Dixon QCSI images of the lumbar spine during treatment in patient 2, where reappearance of fatty marrow is depicted. The coloring of bone marrow in an age and sex matched healthy subject is added to the figure.



a.Aug '93 F_f = 0.22 | b.Sep '94 F_f = 0.19 | c.Oct '95 F_f = 0.34 | d.Jul '98 F_f = 0.41 | e.Jul '99 F_f = 0.45 | f. | g. F_f = 0.44

Figure 1. Increase in bone marrow fat-fraction in the lumbar spine during enzyme therapy in patient 2 (female).
a) just before therapy, at the age of 47 years.
b-e) during therapy; acquisition dates and averaged *F* values of L3-L5 are given.
f) color fat-fraction scale from black (*F* = 0.00) through yellow (0.50) to white (1.00).
g) fat-fraction image of a healthy female volunteer, aged 48.

During enzyme therapy, fat-fractions gradually increased in all patients except in patient 9 (Figure 2). A statistically significant increase in fat-fraction was already apparent after 1 year of treatment (p = 0.007). After 4 to 5 years of treatment, 11 of 12 patients had a normal bone marrow fat-fraction. One patient (patient 3) still had a low bone marrow fat-fraction of 0.18. In contrast, fat-fractions did not change in the untreated Gaucher controls during 2 years of follow-up (P=0.5 and 0.6 at 1 and 2 years, respectively; Figure 2). Patient 9, who experienced a bone crisis located in the lumbar spine, had an abnormal high fat-fraction before treatment, possibly due to fatty replacement after infarction. After 2 years of treatment, the marrow fat-disappeared as a result of collapse of his lumbar vertebrae. In the years thereafter, a gradual reappearance of fatty marrow occurred (Figure 3).

Changes in bone marrow fat-fractions in relation to overall respons

All patients showed decreases in splenic and hepatic volumes (Table 2). Platelet respons was slow in patients 4 and 12, both with large spleens. Six of 11 patients who initially received a dose of 15 U/kg per month had a dose increase as a result of insufficient respons between 6 months and 4 years of treatment (patients 4, 6, 8, 9, 10, and 12, including the most severely affected patients). The dose change is depicted in Figure 2.

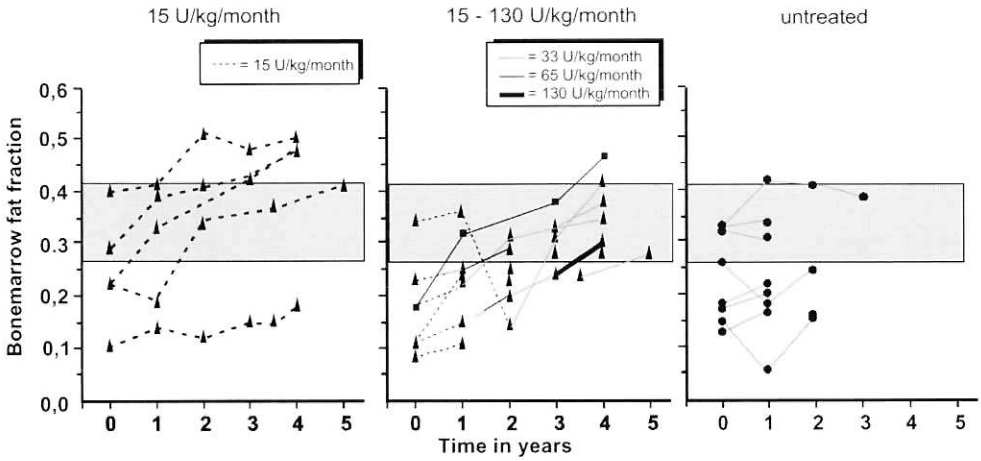
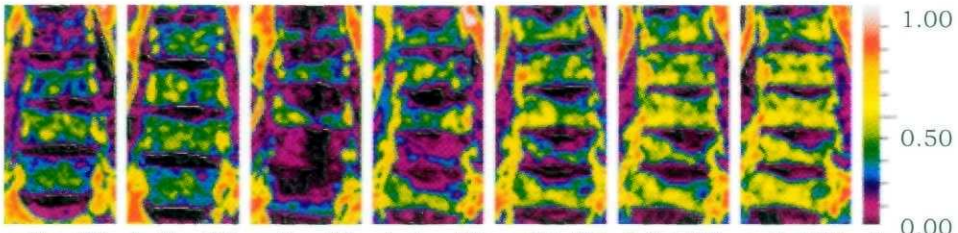


Figure 2. Bone marrow fat-fractions in treated and untreated type 1 Gaucher disease patients. Treated patients without a dose increase (left) and with a dose increase (middle) and untreated Gaucher controls (right). Stippled area, control range.

Improvement in fat-fractions were not clearly affected by a dose increase, but the number of patients is too small to draw any firm conclusions. It is clear that patient 1, who received an initial higher dose, had the most robust increase in fat-fraction. Comparison of the patients who had a dose increase with the patients on persistent low dose reveals that patients with a dose increase were generally more severely affected and also had slightly lower bone marrow fat-fractions before treatment (median 0.13 versus 0.26, p = 0.08, patient 9 excluded). The rate of improvement in fat-fractions during treatment did not differ for both groups.



a. Nov '93 F_f = 0.34 b. Nov '94 F_f = 0.36 c. Nov '95 F_f = 0.14 d. Jan '97 F_f = 0.31 e. Oct '97 F_f = 0.42 f. Oct '98 F_f = 0.47 g. Oct '99 F_f = 0.48 h.

Figure 3. Change in bone marrow fat-fraction in the lumbar spine during enzyme therapy in patient 9. Very high fat-fractions were measured after bone crises in the lumbar vertebrae. After 2 years of treatment, collapse of all lumbar vertebrae occurred.
a) just before therapy.
b-g) during therapy; acquisition dates and averaged *F* values of L3-L5 are given.
h) color fat-fraction scale from black (F = 0.00) through yellow (0.50) to white (1.00).

Discussion

Bone marrow fat-fractions are decreased in the majority of adult type 1 Gaucher disease patients and normalize during treatment with enzyme supplementation. Although it is known that fat-fractions in the normal population increase slowly with age [17,18], comparison with bone marrow fat-fraction measurements in untreated Gaucher controls reveals that in the latter group of patients no significant change is apparent. It is shown that improvement in bone marrow fat-fractions upon therapy is already seen after only 1 year of treatment. An earlier study on the changes in bone and bone marrow upon enzyme therapy has reported significant improvements by different techniques after 42 months of treatment [7]. In the same study, fat-fraction determination by Dixon QCSI was also used as a tool to measure bone marrow infiltration. Significant increases in fat-fractions were observed after 42 months and normalization of bone marrow fat content was achieved in 7/11 patients. The value of these observations is, however, limited by the fact that 6/12 patients are children, in whom a natural shift from red to yellow marrow with age occurs [18,19]. No control population was included in this study to assess the fat-fractions in untreated patients. In our study only adult patients have been included and follow-up of untreated patients serve as controls to correct for changes that may occur during aging. Although the follow-up of these untreated controls is short, it is clear that most patients remained stable or had a decrease in fat-fraction which probably

reflected progressive Gaucher cell infiltration. Only 1 untreated Gaucher control, who had a normal initial fat-fraction, had an unexplained spontaneous increase, possibly related to interruption of menstrual bleeding by menopause. The lack of change in these untreated control patients compared to the significant increase in fat-fractions upon enzyme therapy after 12 months of treatment confirms the value of fat-fraction measurement for the assessment of Gaucher cell infiltration in the bone marrow and the bone marrow respons to treatment.

A pitfall in the interpretation of bone marrow fat-fractions may be the occurence of bone crises with fatty replacement of necrotic areas [10]. These abnormalities can occur in the lumbar spine and may result in high fat-fractions, despite the presence of severe bone disease. Caution must be taken in these cases. Also, in patients with already collapsed vertebrae, the interpretation of the much smaller region of interest may be difficult as depicted in Figure 3.

Earlier studies on the effect of enzyme therapy on bone disease has shown that it takes years of treatment before changes can be established [8,9]. In addition, studies on levels of exogenous administered glucocerebrosidase suggest that a smaller portion of the enzyme is taken up by the bone marrow compared to the liver [20]. Based on these observations, it has been suggested that Gaucher cells in the bone marrow are less easily cleared than storage cells in the liver and spleen and that for accurate treatment of bone marrow involvement large doses of enzyme will be needed [7]. However, the fact that skeletal abnormalities do not rapidly change does not reflect the changes in the bone marrow. A more rapid bone marrow respons is also suggested by earlier observations that low platelet counts and hemoglobin levels as a result of bone marrow failure in splenectomized patients show immediate rise after the initiation of enzyme therapy [9]. Therefore, it is more likely that the techniques applied to evaluate bone disease in type 1 Gaucher disease, such as plain X rays, dexa scans, and quantitative CT, are too insensitive to detect early changes. The present data support the fact that changes in bone marrow involvement may occur as early as 12 months after the initiation of treatment. In addition, it is shown that early and continuing marrow responses occur even with low doses of enzyme. Whether high doses of enzyme result in an even faster increase in bone marrow fat-fractions remains to be determined. The one patient on a relatively higher dose in

our study also had a very quick increase in fat-fraction. In our approach, doses have been adjusted on an individual basis, which implied that several patients (5/11) had a dose increase up to 30 to 120 U/kg per month. All patients had the same rate of improvement of bone marrow fat-fractions, but the patients that had sufficient and sustained responses to the low dose were the less severely affected patients. The question whether there is a dose dependency in the respons cannot be solved in the present study. Individualized dosing is based upon the supposition that there is indeed an effect of dose. The high interindividual variability in respons requires comparative studies in large patient populations to prove that this is indeed the case. Studies in large patient cohorts, possibly with the use of sensitive plasma markers, may eventually enlighten us regarding this issue.

Comparison of our data at 4 to 5 years with the results in the study by Rosenthal et al. [7] after 42 months shows that normalization of fat-fractions can be achieved in the majority of patients in both groups. It is, however, possible that the patients in Rosenthal's study were generally more severely affected than in our study.

Individualized dosing of enzyme supplementation therapy for Gaucher disease depends on an accurate measurement of respons to allow dose adjustments. Since bone disease may produce severe complaints and irreversible damage, it is of critical importance that bone marrow respons can be estimated early in the course of treatment. Fat-fraction determination by Dixon QCSI seems to provide an excellent tool to accomplish this, since we have found that low bone marrow fat-fractions are related to the occurrence of bone complications [16]. We have now implemented this method in our standard protocol and perform these measurements on a yearly basis. Doses of enzyme are increased when fat-fractions do not increase sufficiently or do not normalize within 3 to 4 years of treatment.

In conclusion, fat-fraction determination of the bone marrow of the lumbar spine in type 1 Gaucher disease patients reflects Gaucher cell infiltration and shows early respons to treatment. Although the technique is not (yet) widely available, it seems to be the modality of choice for the assessment of bone marrow involvement.

REFERENCES

1. Beutler E, Grabowski G. Gaucher disease. In: Scriver CR BA, Sly WS, Valle D, ed. The metabolic basis of inherited disease. New York: McGraw-Hill Publishing Company, New York, 1995; 2641-2670.
2. Stowens DW, Teitelbaum SL, Kahn AJ, Barranger JA. Skeletal complications of Gaucher disease. Medicine 1985; 64:310-322.
3. Barton NW, Brady RO, Dambrosia JM, et al. Replacement therapy for inherited enzyme deficiency - Macrophage targeted glucocerebrosidase for Gaucher's disease. N Engl J Med 1991; 324:1464-1470.
4. Figueroa ML, Rosenbloom BE, Kay AC, et al. A less costly regimen of alglucerase to treat Gaucher's disease. N Engl J Med 1992; 327:1632-1636.
5. Hollak CEM, Aerts JMFG, Goudsmit R, et al. Individualized low dose alglucerase therapy for type 1 Gaucher disease. Lancet 1995; 345:1474-1478.
6. Rosenthal DI, Scott JA, Barranger JA, et al. Evaluation of Gaucher disease using magnetic resonance imaging. J Bone Joint Surg 1986; 68A:802-808.
7. Rosenthal D, Doppelt S, Mankin H, et al. Enzyme replacement therapy for Gaucher disease: skeletal responses to macrophage-targeted glucocerebrosidase. Pediatrics 1995; 96(4):629-637.
8. Belmatoug N, Billette de Villeneur T. Skeletal response to enzyme replacement therapy for type 1 Gaucher disease: a preliminary report of the French experience. Semin Hematol 1995; 32(suppl 1):33-38.
9. 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(2):104-111.
10. Stowens DW, Teitelbaum SL, Kahn AJ, Barranger JA. Skeletal complications of Gaucher disease. Medicine (Baltimore). 1985; 64(5):310-322.
11. Miller SPF, Zirzow GC, Doppelt SH, Brady RO, Barton NW. Analysis of the lipids of normal and Gaucher bone marrow. J Lab Clin Med 1996; 127:353-358.
12. Daniels LB, Glew RH. β glucosidase assays in the diagnosis of Gaucher's disease. Clin Chem 1982; 28:569-577.
13. Aerts JMFG, Donker Koopman WE, Koot M, Barranger JA, Tager JM, Schram AW. Deficient activity of glucocerebrosidase in urine from patients with type 1 Gaucher disease. Clin Chim Acta 1986; 158:155-164.
14. Maas M, Dijkstra PF, Akkerman EM. Uniform fat-suppression in hands and feet through the use of two point Dixon chemical shift imaging. Radiology 1999; 210:189-193.

15. Akkerman EM, Maas M. A region growing algorithm to simulutaneously remove dephasing influences and seperate fat and water in two point Dixon imaging. Proceedings of the Society of Magnetic Resonance and the European society for Magnetic Resonance and Biology 1995; 649.
16. Maas M, Akkerman EM, Venama HW, Stoker J, den Heeten GJ. Dixon quantitative chemical shift MRI for bone marrow evaluation in the lumbar spine: A reproducibility study in healthy volunteer. J Comp Assist Tomogr 2001; 25(5):691-697.
17. Ishijima H, Ishizaka H, Horikoshi H, Sakurai M.Water fraction of lumbar vertebral bone marrow estimated from chemical shift misregistration on MR imaging: normal variations with age and sex. Am J Roentgenol 1996; 167(2):355-358.
18. Dooms GC, Fisher MR, Hricak H, Richardson M, Crooks LE, Genant HK. Bone marrow imaging: magnetic resonance studies related to age and sex. Radiology 1985; 155:429-432.
19. Vogler JB 3rd, Murphy WA. Bone marrow imaging. Radiology 1988; 168(3):679-693.
20. Beutler E, Kuhl W, Vaughan LM. Failure of alglucerase infused into Gaucher disease patients to localize in marrow macrophages. Mol Med 1995; 1(3):320-324.