Skeletal Radiol (1993) 22:247–251

Skeletal Radiology

MR imaging in adults with Gaucher disease type I: evaluation of marrow involvement and disease activity

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Abstract. An investigation was conducted to determine the usefulness of magnetic resonance imaging (MRI) in the evaluation of bone marrow involvement in patients with Gaucher disease type I. T1- and T2-weighted images were obtained of the lower extremities of 29 adult patients. Patients were classified into one of three groups based on marrow signal patterns on T1- and T2-weighted images as well as change in signal intensity from T1- to T2-weighted images. An increase in signal intensity from T1- to T2-weighted images was the criterion for an "active process" within the bone marrow. Classification of the 29 patients produced the following results: group A: normal, 4 patients; group B: marrow infiltration, 16 patients; group C: marrow infiltration plus active marrow process, 9 patients. Correlation with clinical findings revealed that all nine patients with evidence of an active marrow process on MRI (group C) had acute bone pain. Conversely, only one of the remaining 20 patients (groups A and B) had bone pain. There was no correlation between disease activity and findings on conventional radiographs. We conclude the MRI provides an excellent noninvasive assessment of the extent and activity of marrow involvement in type I Gaucher disease.

Key words: Gaucher disease – Magnetic resonance imaging – Bone marrow

Gaucher disease type I is the most frequent storage disease and the most prevalent genetic disorder among Ashkenazi Jews. The disease results from numerous mutations at the genetic locus encoding the enzyme glucocerebrosidase (glycosylceramidase cerebroside β glucosidase). These mutations lead to the defective activity of this lysosomal hydrolase [2, 4, 9, 20]. The major visceral manifestations are due to the accumulation of glucocerebrosides, primarily within cells of monocyte/macrophage lineage [7]. The bone marrow and tissue accumulation of glucocerebroside-laden macrophages, i.e., Gaucher cells, leads to anemia, thrombocytopenia, hepatosplenomegaly, and diffuse bony abnormalities [1, 10, 14, 17]. Since conventional radiography is inadequate to assess the presence and extent of involvement of the bone marrow, magnetic resonance imaging (MRI) studies were performed to evaluate the extent and pattern of marrow infiltration. Increased signal intensity on T2-weighted images suggested evidence of active disease or an active process within the marrow. The results were correlated with the clinical assessment of disease activity based on the presence of bone pain.

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Materials and methods

The diagnosis of Gaucher disease type I was established in all patients by the deficiency of glucocerebrosidase activity in peripheral blood leukocytes and cultured skin fibroblasts [10]. In addition, Gaucher cells were demonstrated within iliac crest bone marrow aspirates or biopsies. MRI of the pelvis and both thighs was performed on a Gyrex 5000 Superconducting Elscint Scanner operating at 0.5 tesla. In each case, a body coil was employed, obtaining images in the coronal or sagittal plane. Data were collected on a 256×256 matrix and interpolated to 512×512 for display. Section thickness varied between 7 mm and 10 mm. The area for evaluation included the entire length of the femur from the hips through the knees. Spin echo pulse sequences were used. On T1-weighted images, TR ranged from 350 to 500 ms and TE from 26 to 30 ms. On the T2-weighted images, TR ranged from 1800 to 2000 ms and TE from 60 to 80 ms.

Based on changes in marrow signal intensity on T1- and T2-weighted images as well as an increase in signal intensity from T1 to T2, the patients were classified into three different groups (Table 1):

Group A: Normal – High (normal) signal intensity on T1- and T2-weighted images, with no increase in signal intensity from T1 to T2 (Fig. 1).

Group B: Marrow infiltration – Decreased signal intensity on both T1- and T2-weighted images, with no increase in signal intensity from T1 to T2 (Fig. 2).

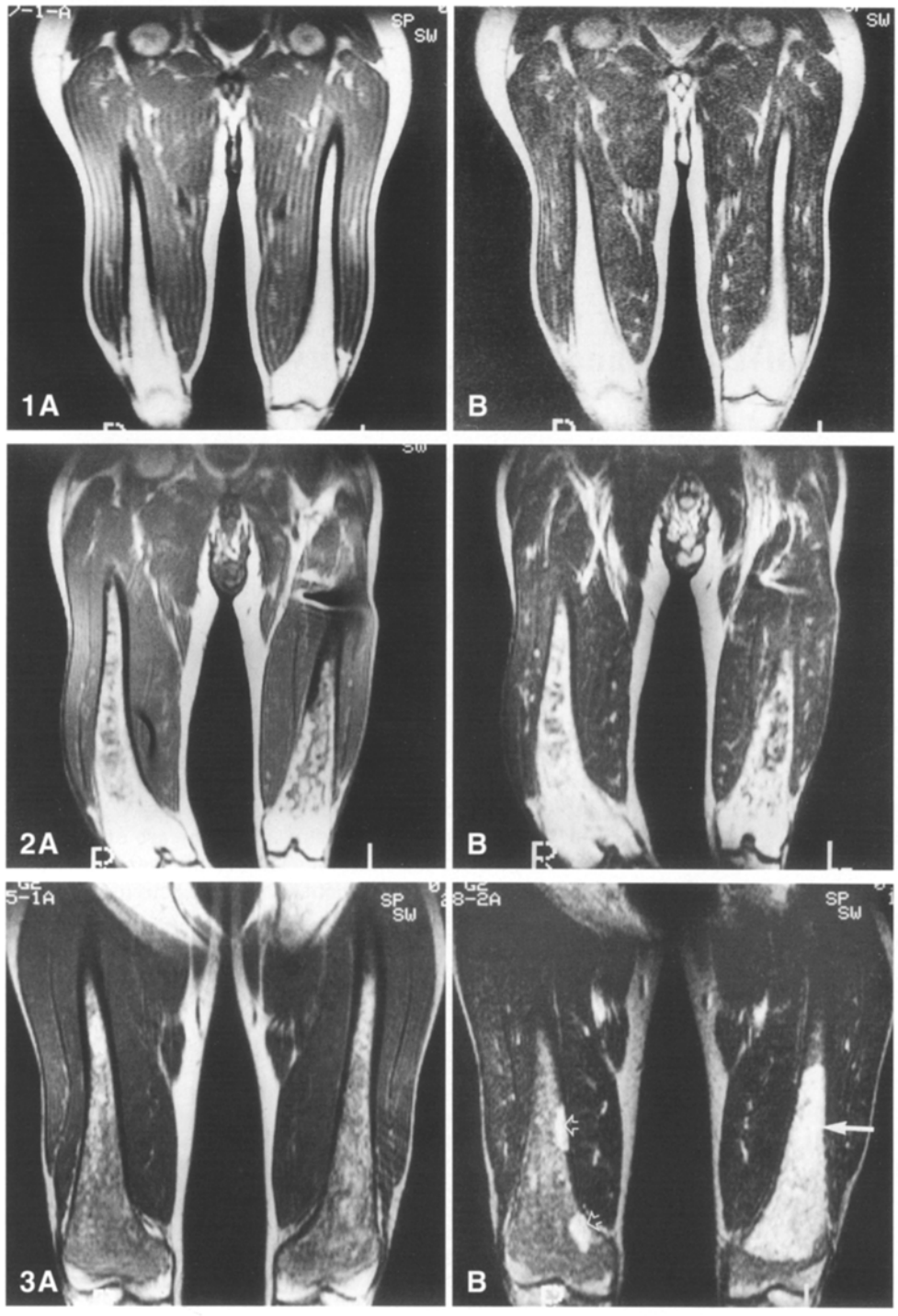

Fig. 1A, B. Normal (group A). T1- (**A**) and T2-weighted images (**B**) show normal high signal intensity in the marrow cavity

Fig. 2A, B. Marrow infiltration (group B). T1- (**A**) and T2-weighted images (**B**) show decreased signal intensity of the marrow cavity. There is no change in signal intensity from T1 to T2

Fig. 3. Marrow infiltration plus active marrow process (group C). T1- (**A**) and T2-weighted images (**B**) show decreased signal intensity in the marrow cavity. The T2-weighted image shows areas of increased signal intensity (*arrows*)

Group C: Marrow infiltration plus marrow processes – Decreased homogeneous signal intensity on both T1- and T2-weighted images, with increase in signal intensity from T1 to T2 (Fig. 3).

The epiphysis was judged to be normal if it displayed a high signal intensity on T1- and T2-weighed images and abnormal if it had a low signal intensity.

Plain radiographs of the skeleton were classified as follows (modification of previously described classification [11]):

0: Normal

1: Slight X-ray change – diffuse osteoporosis

2: moderate X-ray change – medullary expansion with localized destruction, loss of normal concavity of distal femoral shaft, endosteal cortical erosions

3: severe X-ray change – ischemic necrosis with diffuse destruction, patchy densites and erosions, sclerotic streaks, and periostitis sequestra; epiphyseal flattening or destruction; mixed lytic and sclerotic "soap bubble" pattern.

Clinical findings were recorded by the clinician (GG) caring for the patient. The presence or absence of bone pain was recorded without knowledge of the MRI findings.

Table 1. Magnetic resonance imaging of bone marrow involvement in type I Gaucher disease (29 patients)

Group	T1-weighted image	T2-weighted image	T1→T2	Pattern
A	Normal	Normal	No change	Normal
B	Decreased signal	Decreased signal	No change	Marrow infiltration
C	Decreased signal	Decreased signal	Increase	Marrow infiltration plus active marrow process

Results

MRI examinations were performed on 29 adult patients. The patients' ages ranged from 21 to 72 years (average age 39.8 years). There were 16 male and 13 female patients. The results are listed in Table 2.

Classification of patients into groups based on MRI findings produced the following results:

Group A (normal): 4 patients
Group B (marrow infiltration): 16 patients
Group C (marrow infiltration plus active marrow process): 9 patients

Among the cases in groups B and C we observed minor variations in the homogeneity of the signal intensity within the marrow. As these were minor variations, the patients were not further divided into subgroups based on these differences.

Correlation of the MRI classification with X-ray findings showed the following:

Group A: 4/4 patients had grade 0 X-ray (normal X-ray)
Group B: 1/16 – grade 0 X-ray (normal)
4/16 – grade 1 X-ray (mild change)
1/16 – grade 2 X-ray (moderate change)
7/17 – grade 3 X-ray (severe change)
(Three patients did not undergo X-ray.)
Group C: 1/9 – grade 1 X-ray (mild change)
8/9 – grade 3 X-ray (severe change).

Epiphyses were spared in 16 cases and involved in 13 cases. In group A, none of the four cases had epiphyseal involvement. In group B, the epiphyses were involved in 6/16 cases. In group C, the epiphyses were involved in 7/9 cases.

Correlation with clinical findings showed that none of the four patients in group A had bone pain, one of the 16 patients in group B had bone pain, and all nine of the patients in group C had bone pain.

Table 2. Results for all 29 patients

Patient	Sex/ age (years)	T1-weighted image	T2-weighted image	T1→T2	Pattern (group)	Epiphysis	X-ray[a]	Pain
1	F/21	Decreased	Decreased	No change	B	Spared	1+	None
2	M/21	Normal	Normal	No change	A	Spared	0	None
3	F/22	Decreased	Decreased	Increase	C	Involved	3+	Acute pain lower extremities
4	M/23	Decreased	Decreased	Increase	C	Involved	3+	Acute pain lower extremities
5	F/26	Decreased	Decreased	No change	B	Spared	–	None
6	F/27	Decreased	Decreased	No change	B	Spared	0	None
7	F/28	Normal	Normal	No change	A	Spared	0	None
8	M/28	Decreased	Decreased	Increase	C	Involved	3+	Acute pain lower extremities
9	M/29	Normal	Normal	No change	A	Spared	0	None
10	F/29	Decreased	Decreased	Increase	C	Involved	3+	Acute pain lower extremities
11	F/31	Decreased	Decreased	Increase	C	Involved	3+	Acute pain lower extremities
12	M/32	Decreased	Decreased	Increase	C	Involved	3+	Acute pain lower extremities
13	F/35	Decreased	Decreased	No change	B	Spared	–	None
14	F/36	Decreased	Decreased	No change	B	Spared	3+	None
15	M/39	Decreased	Decreased	No change	B	Involved	3+	None
16	M/39	Decreased	Decreased	No change	B	Involved	3+	None
17	M/41	Decreased	Decreased	Increase	C	Spared	1+	Acute pain, lower extremities
18	M/41	Normal	Normal	No change	A	Spared	0	None
19	F/43	Decreased	Decreased	No change	B	Involved	1+	None
20	F/44	Decreased	Decreased	Increase	C	Spared	3+	Acute pain, lower extremities
21	F/46	Decreased	Decreased	No change	B	Involved	3+	None
22	M/46	Decreased	Decreased	No change	B	Involved	3+	None
23	M/51	Decreased	Decreased	No change	B	Spared	2+	None
24	F/61	Decreased	Decreased	No change	B	Spared	1+	None
25	M/66	Decreased	Decreased	No change	B	Involved	3+	None
26	M/66	Decreased	Decreased	No change	B	Spared	3+	None
27	M/68	Decreased	Decreased	No change	B	Spared	–	None
28	M/72	Decreased	Decreased	Increase	C	Involved	3+	Acute pain, lower extremities
29	M/78	Decreased	Decreased	No change	B	Spared	1+	None

[a] 0, Normal; 1, slight change; 2, moderate change; 3, severe change

Discussion

Although the most prevalent radiological manifestations of Gaucher disease type I are skeletal abnormalities, as many as one-third of the affected patients do not show clear radiological changes [17]. Skeletal alterations may range from mild osteopenia, through moderate osteosclerosis, to crippling deformities due to pathological fractures of both the axial and the peripheral skeleton [1, 3, 6, 10, 18]. Since minor bone loss, early erosions, and marrow replacement by Gaucher cells are usually undetectable by conventional radiographs, attempts have been made to visualize marrow replacement and to predict the severity of the disease using computed tomography and technetium-99m sulfur colloid scintigraphy [11, 13].

Normally, the adult bone marrow is composed of 80% fat, 15% water, and 5% protein [19]. Because fat is the major component of marrow, the T1 relaxation time is short and the T2 is relatively long, resulting in high signal intensity on both T1- and T2-weighted images. This normal high signal within the marrow cavity forms the basis for signal alterations produced by tumors and systemic infiltrating processes. Vogler and Murphy [19] classified the various disorders that alter bone marrow patterns on MRI into five different groups. These include: (1) reversal of marrow conversion – yellow marrow reversed to red marrow production; (2) marrow infiltration or replacement; (3) myeloid depletion due to disappearance of cells; (4) bone marrow edema; and (5) bone marrow ischemia. Gaucher disease is unique in that the changes in the bone marrow are a combination of infiltration, edema, and ischemia.

When bone marrow is infiltrated by Gaucher cells, they cause reduction of signal intensity on both T1- and T2-weighted images. This reduction is due to the deposition of glucocerebrosides in the marrow in Gaucher disease. Gaucher-cell-infiltrated bone marrow also contains protein, glycoproteins, and other components which may contribute to the decreased signal intensity of the marrow on both T1- and T2-weighted images [15].

The signal intensity of the involved marrow in Gaucher disease has been reported to be homogeneously or nonhomogeneously decreased [5, 15, 16]. We observed minor variations in the homogeneity of the signal intensity within the marrow. The presumed mechanism for the changes in signal intensity is the replacement of high signal intensity fatty marrow by deposits of Gaucher cells of relatively lower signal intensity. The variation in homogeneity may reflect interpatient variation in this process. Some patients may have a diffuse infiltration and others may have a patchy infiltration, with islands of preserved fatty marrow. This hypothesis would explain why some researchers observed a homogeneous change in signal intensity [15] while others observed a non-homogeneous pattern [16]. We observed minor variations in the homogeneity but did not further classify these variations into subgroups.

On the basis of changes in marrow signal intensity on T1- and T2-weighted images, we classified patients into three groups. Group A consisted of patients with a normal pattern within the marrow cavity. Group B consisted of patients with decreased signal intensity within the marrow on both T1- and T2-weighted images, with no change from T1- to T2-weighted images. We hypothesize that this represents infiltration of the marrow by Gaucher cells. Group C consisted of patients with decreased signal intensity within the marrow on both T1- and T2-weighted images, but a relative increase in signal intensity from T1- to T2-weighted images. It seems to us that this increase in signal intensity corresponds to some "active process" within the bone marrow. Correlation with clinical findings showed that only one of the 20 patients comprising groups A and B had bone pain, while all nine patients in group C had bone pain.

In our study, we considered a relative increase in signal intensity on T2-weighted images as evidence of an "active process" within the marrow. While the term "active process" is nonspecific, this finding did correlate well with the patient's symptoms. The use of a nonspecific term such as "active marrow process" seems justified in evaluating the marrow changes in Gaucher patients. The bone pain experienced by patients with Gaucher disease is poorly understood. The likely mechanism is accumulation of glucocerebrosides and glucocerebroside-laden macrophages (Gaucher cells) within the bone marrow. This accumulation produces intramedullary extravascular compression, with vascular obstruction and secondary ischemic events. The exact pathologic correlate for the pain experienced by these patients has not been determined. The increased signal intensity on T2-weighted images may correspond to increased water within the marrow cavity in areas of edema associated with acute infarction. This would correspond to the bone marrow edema pattern described by Vogler. Recently, Horev et al. [12] proposed that hemorrhage associated with bone crisis in Gaucher disease can cause high signal on T1- and T2-weighted images. While the exact cause of the increase in signal intensity on T2-weighted images can at this point only be speculated upon, this finding does correlate well with the patient's symptoms. Conventional X-ray, however, cannot demonstrate any alteration in the bony structure in the acute stage.

The epiphyseal region was spared in all four patients in group A. The epiphysis, however, was involved in six of the 16 patients in group B and seven of the nine patients in group C. In general, our findings correspond with those of Lanir et al. [15] and Rosenthal et al. [16], who reported that the epiphyses were generally spared unless the involvement of bone was extensive.

Our results suggest that MRI is a valuable noninvasive modality in evaluating the extent of bone marrow involvement and assessing disease activity in type I Gaucher disease. We have presented a classification scheme which correlates well with clinical findings. At the present time these results are largely of academic interest. With the recent implementation of enzyme replacement therapy for Gaucher disease, however, MRI of the skeletal system may in the future have clinical value in assessing response to treatment and determining correct replacement dose.

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