The Use of Specialist Imaging in the Evaluation of Disease Extent and Response to Treatment in Gaucher Disease

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Purpose

Gaucher disease is a rare autosomal recessively inherited metabolic disorder with multiple skeletal manifestations, which are often the most disabling aspect of the disease. This presentation will provide an overview of currently used imaging techniques in the diagnosis, evaluation and monitoring of the disease. There will be an emphasis on how magnetic resonance imaging (MRI) can be used to assess the extent and severity of Gaucher disease, focusing in particular on the use of serial imaging to monitor and quantify the response to treatment with enzyme replacement therapy.
Methods and Materials

Gaucher’s disease (GD) is a rare inherited disorder caused by a defect in the gene responsible for producing the enzyme lysosomal glucocerebrosidase. This results in a failure to metabolise glucocerebroside, a cell membrane constituent of red and white blood cells. The protein accumulates in macrophages which are subsequently deposited in tissues as Gaucher cells.

There are three clinical subtypes:-

(1) Non-neuropathic form - Commonly presents in childhood with hepatosplenomegaly, pancytopenia, and skeletal disease. It is the most common lysosomal storage disorder and the commonest genetic condition in the Ashkenazi Jewish population.

(2) Acute neuronopathic form - Associated with severe neurological complications and causes death during infancy or early life.

(3) Chronic neuronopathic form - Intermediate form with progressive neurologic manifestations starting to appear in the second or third decade.

Type 1 disease is the most common form and affects the skeletal system. This presentation will now discuss the imaging techniques used to diagnose and monitor Type 1 GD.
Results

1. IMAGING FEATURES OF GAUCHER DISEASE

RADIOGRAPHY

Radiography has a low sensitivity (30-40%) for defining the extent and distribution of disease activity in Gaucher disease [1]. Its use is therefore limited to detection of skeletal complications, such as remodelling deformities and fractures, and for pre- and post-operative evaluation of joint arthroplasty. In addition, characteristic but non-specific findings on the plain radiograph may provide early clues to the diagnosis of GD, particularly in developing countries where access to cross-sectional imaging modalities is limited.

Abnormal remodelling - Erlenmeyer flask deformity - This results from impairment of bone remodelling in the distal femur and proximal tibia. The classical appearance is of constriction of the diaphysis and flaring of the metaphysis to give a shape which resembles an Erlenmeyer flask [Fig. 1 on page 10]. Up to 80% of adult patients with GD are likely to have a remodelling deformity in this location, however it should be noted that this appearance is not specific for GD and therefore without other confirmatory investigations it cannot be used to make a firm diagnosis.

Osteopaenia - Osteopaenia is present in nearly all patients with Gaucher's disease [Fig. 2 on page 10]. Cortical thinning results from bone marrow expansion and is therefore often, although not exclusively, seen in areas of marrow infiltration. The pattern of bone involvement can however be either focal or diffuse.

Bone infarction and osteonecrosis - Patients with GD are at risk of developing chronic ischaemia of bone which leads ultimately to osteonecrosis, also known as avascular necrosis. This can take either of two radiographic forms depending on its location. Occlusion of medullary blood vessels and subsequent medullary infarction leads to death of Gaucher cells and formation of an insoluble calcium soap [2]. This is seen as increased medullary density and gives rise to a 'bone within bone' appearance on radiographs. When osteonecrosis occurs at the hip the result is fragmentation of the femoral head and extensive sclerosis due to the same underlying pathological process [Fig. 3 on page 11]. It should be noted that early bone ischaemia is better appreciated on MRI, as the plain radiographic features described are the result of irreversible bone death.
Bone pain and pathological fractures - Increased bone resorption, cortical thinning and osteopenia results in an increased incidence of pathological fractures in patients with GD. Stress fractures, vertebral collapse and kyphosis can occur. Bone pain can also be due to ischaemia and oedema within bone marrow as a result of infiltration by Gaucher cells. As many as 66% of patients with Type 1 disease suffer from episodic or chronic bone pain.

Bone crises - Up to a third of GD patients suffer from bone crises, characterized by episodes of acute, severe skeletal pain, usually accompanied by fever, tachycardia and an elevated white blood cell count [2]. Plain radiography and CT may demonstrate elevation of the periosteum in the affected bone [ Fig. 4 on page 12 ], and there may be high T2 weighted MRI signal. The signs, symptoms and imaging features are very similar to that of osteomyelitis, which also occurs with greater frequency in GD. Differentiation between the two conditions is often challenging but important because of the need for prompt treatment with antibiotics and/or surgical drainage in cases of osteomyelitis.

MAGNETIC RESONANCE IMAGING (MRI)

MRI is the mainstay of skeletal imaging in GD. It can be used to detect the presence of disease, assess the severity of disease, identify complications and monitor the response to treatment.

Protocols used for MR imaging of GD varies between institutions but should include imaging of the abdomen, to assess hepatosplenomegaly, and in children additional lower limb sequences are used due to natural bone marrow changes making assessment difficult.
**MRI Gaucher protocol**

- T1 or T2 axial images through upper abdomen
- T1 and STIR sagittal images lumbar spine
- T1 and STIR coronal images pelvis
- T1 and STIR coronal images femora
- In children and adolescents:
  - All of the above +T1 and STIR coronal images tibia

**Fig. 5**: The MRI protocol used at our National Centre for Gaucher Disease

**References**: Radiology Department, Royal Free Hospital NHS Trust, Royal Free Hospital - London/UK

**Bone marrow infiltration** - Infiltrated bone marrow in GD appears as low signal intensity on T1 and non-fat-suppressed T2 and T2*-weighted sequences relative to subcutaneous fat. On fat-suppressed sequences such as STIR infiltrated bone marrow appears relatively hyperintense. The pattern of involvement can be homogeneous or heterogenous [3]. [Fig. 6 on page 14 ].

**Osteonecrosis** - Irreversible death of bone tissue. The pathophysiology of osteonecrosis in GD is not completely understood, but it is thought to occur due to ischaemia secondary to chronic infarction. The most commonly affected sites are in the femoral head, proximal femora and vertebral bodies.

The progressive changes seen in osteonecrosis on MRI can be described using the Mitchell classification. In this system, Class A appears as a high intensity T1-weighted signal and an intermediate intensity T2 signal, similar to the appearance of fat. Class B produces high intensity T1- and T2-weighted signal, indicating blood infiltration. Class C corresponds to oedema and appears as low intensity T1-weighted and high intensity T2-weighted signal. Finally, Class D is seen as low intensity T1- and T2-weighted signal due to replacement of necrosed components with fibrous tissue. Areas of established bone infarction appear similar to those seen in sickle patients, with well demarcated serpiginous areas of hypointense T1 and T2-weighted signal [ Fig. 9 on page 16 ].
2. QUANTIFYING AND MONITORING DISEASE

Treatment of GD with enzyme replacement therapy (ERT) has been demonstrated to achieve a significant reduction in subsequent skeletal complications, including bone pain, bone crises, infarction and pathological fractures [4]. Complications such as osteonecrosis and vertebral compression cannot however be reversed, underlining the need for early recognition of disease and initiation of therapy.

SERIAL MRI IMAGING

T1-weighted MRI is the most widely used imaging technique to assess the severity of GD and to monitor response to therapy. In patients with GD normal bone marrow is replaced by Gaucher cells, demonstrated as low T1-weighted signal in affected bones. Following treatment with ERT, the return of fat marrow leads to a dramatic increase in the T1-weighted signal [1]. [Fig. 10 on page 17, Fig. 11 on page 18, Fig. 12 on page 19, Fig. 13 on page 20]

Assessment of bone marrow changes in children and adolescents can be particularly challenging, due to the normal pattern of red to lipid-rich yellow marrow conversion with aging [Fig. 14 on page 20]. As this process occurs in a centripetal pattern, in children supplementary imaging of the lower leg should be used to evaluate disease severity.

Another advantage of serial MRI imaging with modern software is that it can be used to accurately measure changes in liver and spleen size in response to treatment [Fig. 12 on page 19].

QUANTITATIVE AND SEMI-QUANTITATIVE TECHNIQUES

Quantitative chemical shift imaging (QCSI) - This is the most accurate and only truly quantitative way of measuring the extent of bone marrow disease in GD. It measures the fraction of bone marrow that is fat by using the difference in resonant frequencies of fat and water. [Fig. 15 on page 21] The technique has been shown to correlate well with disease activity and is both accurate and reproducible [5]. The major disadvantages of QCSI are that the technology is not widely available and a dedicated MR physicist is required in addition to a radiologist.
Fig. 15: Quantitative Chemical Shift Imaging (QCSI) is used to accurately quantify fat content in bone marrow of GD patients.


Bone Marrow Burden (BMB) score - This is an MRI based scoring system which assigns points based on the sites of disease involvement and its characteristics on T1 and T2 weighted images [6]. Up to 8 points may be allocated on evaluation of the femora and a further maximum of 8 points on evaluation of the lumbar spine, giving a total score out of 16. The higher the BMB score, the greater the extent of bone marrow involvement [Fig. 16 on page 22]. Whilst not as accurate or sensitive as QCSI, the use of BMB score is advantageous in that it is easy to apply to standard MRI images and has been shown to be have good inter-observer reliability.

Vertebra-disc ratio (VDR) - This is the ratio of the signal intensity of the L3 vertebra to a healthy L3/4 intervertebral disc. Patients with GD have been shown to have a reduced VDR compared with healthy subjects. The clinical significance of this and its application in monitoring disease is still being evaluated [1].

Other scoring systems - Several other bone marrow disease burden scoring systems based on standard MRI images have been proposed and continue to be evaluated. These include the Rosenthal staging system, the Dusseldorf score and the Terk classification [3]. Although they differ in terms of the method used to arrive at a score or classification, these systems are all based on establishing how much bone marrow is involved and also
its location in the skeleton. The site of involvement is important because in GD bone marrow infiltration spreads in a predictable manner starting in the axial skeleton and progressing to the proximal and then distal appendicular skeleton.

**Dual Energy X-ray Absorptiometry (DEXA)** - widely used to assess bone mineral density (BMD), particularly in post-menopausal women. Published data suggests that DEXA can also be used to assess and monitor the severity of osteopaenia in GD. The presence of focal lesions, osteonecrosis and infarcts can confound the results however, and correlation between BMD score on DEXA in GD patients and the risk of fracture has not yet been proven [7].

**Bone scintigraphy** - Several radionuclide tracers have been used to image bone marrow infiltration, including $^{99m}$Tc-sestamibi, $^{99m}$Tc#sulfur colloid and Xenon-133 [Fig. 17 on page 23]. The most widely used of these in GD patients is $^{99m}$Tc-sestamibi, which accumulates in tissues with a high density and turnover of cells. It is not specific for bone marrow disease, and can therefore be used to assess Gaucher cell infiltration of liver and spleen. A scoring system has been developed that correlates well with BMB scores on MRI [8]. The main disadvantages of using scintigraphy for routine disease monitoring are its poor spatial resolution and the radiation dose, limiting its use particularly in children. $^{99m}$Tc-MDP is one radiotracer that may however be useful in the differentiation between bone crisis and osteomyelitis in the acute setting.
Fig. 1: Erlenmeyer flask deformity

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Fig. 2: Osteopaenia in the proximal femur (Image courtesy of Dr Bruno Bembi, University Hospital Santa Maria della Misericordia, Italy)

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**Fig. 3:** Plain radiograph of the right hip demonstrating the result of bone infarction. There is flattening of the infarcted part of the femoral head, articular collapse and marked sclerosis. (Image courtesy of Dr Bruno Bembi, University Hospital Santa Maria della Misericordia, Italy)

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**Fig. 4:** Stress fracture in a patient with GD. Note the elevated periosteum (arrow).

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**Fig. 5:** The MRI protocol used at our National Centre for Gaucher Disease

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Fig. 6: T1 and T2 weighted sagittal images of the lumbar spine in a patient with GD. There is diffuse marrow infiltration and several collapsed vertebrae.
Fig. 7: T1 and T2 weighted coronal images of the femora. There is focal heterogenous signal change in the left femur due to marrow infiltration.

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Fig. 8: Coronal T1-weighted MR image of the femora. There is diffuse, heterogenous hypointensity throughout both femora and visualised tibiae in keeping with Gaucher infiltration. Note also the bilateral Erlenmeyer flask deformity.

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**Fig. 9:** T1 weighted coronal MRI. The serpiginous abnormalities seen in the distal femora represent areas of bone infarction.

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Fig. 10: Pre-treatment (left) and 2 years post-treatment with ERT T1 weighted images of the lumbar spine. On the pre-ERT scan the signal of the vertebral bodies is almost the same as that of the intervertebral disks. On the post-treatment image the increase in vertebral body signal is due to a return of fatty marrow.

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**Fig. 11:** The same patient as in Fig 7. On the pre-treatment T1 image on the left there is diffuse low signal in the femora, which has improved on the image taken following ERT. Note the bone infarct in the left femur remains unchanged.

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**Fig. 12:** Images of the spleen of a GD patient taken pre- (left) and post (right) treatment with ERT. MRI is an accurate way of measuring changes in volume of the spleen and liver.
Fig. 13: Pre-treatment (left) and post-treatment (right) images of a 27 year old GD patient. There has been a dramatic improvement in the appearance of low T1-weighted signal abnormality in the femora.

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Fig. 14: T1-weighted sagittal MRI of the lumbar spine in a 14 year old boy on the left and an 80 year old man on the right. Neither of these patients has GD or any other bone marrow disease. These signal changes are a normal part of the ageing process.

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**Fig. 15:** Quantitative Chemical Shift Imaging (QCSI) is used to accurately quantify fat content in bone marrow of GD patients.


**TABLE 1**
Evaluation of BMB in the Femora

<table>
<thead>
<tr>
<th>Relaxation Time</th>
<th>Signal Intensity*</th>
<th>BMB Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>Hyperintense</td>
<td>2</td>
</tr>
<tr>
<td>T2</td>
<td>Slightly hyperintense</td>
<td>1</td>
</tr>
<tr>
<td>T2</td>
<td>Isointense</td>
<td>0</td>
</tr>
<tr>
<td>T2</td>
<td>Slightly hypointense</td>
<td>1</td>
</tr>
<tr>
<td>T2</td>
<td>Hypointense</td>
<td>2</td>
</tr>
<tr>
<td>T2</td>
<td>Mixed type</td>
<td>3</td>
</tr>
<tr>
<td>T1</td>
<td>Slightly hyperintense or isointense</td>
<td>0</td>
</tr>
<tr>
<td>T1</td>
<td>Slightly hypointense</td>
<td>1</td>
</tr>
<tr>
<td>T1</td>
<td>Hypointense</td>
<td>2</td>
</tr>
</tbody>
</table>

**TABLE 2**
Evaluation of BMB in the Lumbar Spine

<table>
<thead>
<tr>
<th>Relaxation Time</th>
<th>Signal Intensity*</th>
<th>BMB Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>Hyperintense</td>
<td>2</td>
</tr>
<tr>
<td>T2</td>
<td>Slightly hyperintense</td>
<td>1</td>
</tr>
<tr>
<td>T2</td>
<td>Isointense</td>
<td>0</td>
</tr>
<tr>
<td>T2</td>
<td>Slightly hypointense</td>
<td>1</td>
</tr>
<tr>
<td>T2</td>
<td>Hypointense</td>
<td>2</td>
</tr>
<tr>
<td>T1</td>
<td>Slightly hyperintense</td>
<td>0</td>
</tr>
<tr>
<td>T1</td>
<td>Isointense</td>
<td>1</td>
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<tr>
<td>T1</td>
<td>Slightly hypointense</td>
<td>2</td>
</tr>
<tr>
<td>T1</td>
<td>Hypointense</td>
<td>3</td>
</tr>
</tbody>
</table>

**B: Infiltration Pattern**

<table>
<thead>
<tr>
<th>Pattern</th>
<th>BMB Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patchy</td>
<td>1</td>
</tr>
<tr>
<td>Diffuse</td>
<td>2</td>
</tr>
<tr>
<td>Absence of fat in basivertebral vein region</td>
<td>1</td>
</tr>
</tbody>
</table>

Fig. 16: The components of the Bone Marrow Burden (BMB) scoring system.

© Maas M et al. Radiology 2003; 229:554-561

Fig. 17: 99mTc-sulfur colloid bone marrow scan of a 6 year old. There is marked splenomegaly with abnormal increased uptake in the liver and spleen. There is generalised reduction in marrow activity with areas of total absence of activity, for example, in the mid shaft of the right femur. (Image courtesy of L. Bassioni/P. Anderson, Great Ormond Street Hospital, London)

Conclusion

Radiological imaging has a recognised role in the diagnosis and monitoring of skeletal manifestations of Gaucher disease, as well as in the identification of its complications. Modern imaging techniques, particularly MRI, have proven themselves invaluable in the assessment of treatment response with the ability to provide clinicians with both qualitative and semi-quantitative evaluation of disease extent. These techniques can be used to compare serial examinations with baseline imaging to accurately determine disease progression or resolution and thereby to facilitate clinical management.
References

1. Maas M, Poll LW, Terk MR. Imaging and quantifying skeletal involvement in Gaucher disease. BJR, 75 (Suppl. 1), A13-A24, 2002


