Clinical applications of Dixon chemical shift MR imaging: Morbus Gaucher, Morbus Hansen
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Chapter 1

Introduction
Chapter 1

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**What is Gaucher disease?**

Gaucher disease is the most prevalent of the lysosomal storage disorders. The French pathologist Philippe C. E. Gaucher described this disease for the first time in 1882 as a splenic epithelioma [1]. Later it was noted that the splenic enlargement was caused by storage of lipid material that was identified as a cerebroside in 1924 and as a glucocerebroside (glucosylceramide), a glycolipid, ten years later. The accumulation of the glucocerebroside was found to be due to a deficient activity of a lysosomal enzyme, glucocerebrosidase (glucosylceramidase). The deficient activity of the enzyme results in accumulation of glucocerebroside in macrophages. These lipid-loaded macrophages, so-called Gaucher cells, accumulate mainly in the spleen, liver, and bone marrow [2].

Three phenotypes are recognized on basis of the clinical features of the disease; type 1, non-neuronopathic, type 2, acute neuronopathic, and type 3, subacute neuronopathic [2].

This thesis only involves patients with type 1 Gaucher disease; the most prevalent form. The birth prevalence of Gaucher disease in the Netherlands was calculated for Gaucher disease type 1 as 0.9 per 100.000 and as 1.16 per 100.000 for all types combined [3].

Of the clinical symptoms splenomegaly is the most striking feature, leading to hypersplenism with gradual pancytopenia [2,4-6]. Hepatomegaly is often less dramatic, however, gross enlargement is mostly found in splenectomized patients. The active red bone marrow often is infiltrated with Gaucher cells. As the demand for marrow function increases, so does reconversion of the dormant yellow marrow in the limbs to active red marrow. Eventually these new areas also become packed by Gaucher cells. This may lead to deformities, as the classical Erlenmeyer flask appearance of the distal femurs, representing bone marrow packing, however, not exclusively seen in Gaucher disease [7].
Bone pain and acute bone crisis, or aseptic osteomyelitis that resemble those seen in sickle cell disease may be seen [5,8]. Bone infarcts and avascular necrosis may develop. Eventually in some patients severe progressive and destructive bone disease necessitating joint replacement will occur. It should be noted that the degree of hematological problems and the scale of organomegaly do not always correlate with the severity of bone disease [9]. This necessitates separate evaluation of each compartment for disease activity using a sensitive modality [4,8,10].

The availability of enzyme supplementation therapy (Ceredase ® alglucerase, placentally derived glucocerebrosidase; Cerezyme ® imiglucerase, recombinant glucocerebrosidase; both manufactured by Genzyme Co., MA, USA) has had a great impact on the symptoms of the disease [11]. Intravenous administration of the enzyme results in the breakdown of accumulated glycolipids and, subsequently, in reversal of the manifestations of the disease [12]. Cytopenia improves, and spleen and liver size decrease. Bone disease tends to respond much more slowly, and it is much more difficult to assess skeletal involvement [13]. Whereas there is no doubt about clinical efficacy of enzyme supplementation, several issues remain unclear, such as the criteria for initiating treatment and the best way to monitor effects, especially in the bone marrow compartment. The variability in clinical responses to treatment and the extremely high costs (about $200,000 to $500,000 per patient per year) are important in these respects [11].

**Bone Marrow - A Short Introduction [14]**

Bone marrow is one of the largest organs of the body by weight, approaching 3000 g in adult men and approximately 2600 g in women. Its function is to provide a continual supply of red cells, platelets, and white cells to meet the body's demands for oxygenation, coagulation, and immunity. The basic structure of bone marrow consists of a trabecular framework housing fat cells, covered with hematopoietic cells, supported by a system of reticulum cells, nerves and vascular sinusoids. Cellular marrow constituents include all stages of erythrocytic and leucocytic development, as well as fat cells and reticulum cells. Fat cells are a major component of bone marrow. The size of these cells appears to be responsive to hematopietic activity.
During periods of decreased hematopoiesis, the fat cells increase in volume and number, whereas in increased hematopoiesis fat cells atrophy. Reticulum cells can be divided in two major groups - the phagocytic cell, and the undifferentiated non-phagocytic cell. The phagocytic group consists of macrophages, found predominantly in regions that are hematopoietically active.

"Yellow marrow" is composed predominantly of fat cells (15% water, 80% fat and 5% protein). "Red marrow" is considered hematopoietically active marrow. It contains approximately 40% water, 40% fat and 20% protein (Fig. 1). Virtually the entire fetal marrow space is dedicated to red marrow at birth. In the immediate postnatal period, conversion from red to yellow marrow begins in a predictable and orderly pattern. This conversion begins in the terminal phalanges and progresses from peripheral (appendicular) towards central (axial). In an individual long bone it progresses from diaphysis to metaphysis. The cartilaginous epiphysis and apophysis can be characterized as yellow marrow. By the time a person is 25 years old, marrow conversion is considered complete and the adult pattern is achieved. Red marrow predominantly is concentrated in the axial skeleton and proximal parts of the appendicular skeleton. However, there is a great variation possible, i.e. hematopoietic marrow may occupy up to two-thirds of the femoral shaft. Ultimately, a balanced distribution of red and yellow marrow is achieved. Alterations in the body's demand for hematopoiesis will disturb this balance. With increasing demand for red cells, a reconversion of yellow to red marrow takes place, from axial to appendicular skeleton, in reverse to the conversion pattern.

Figure 1. Bone marrow samples, with haematoxylin and eosin stain, from red cellular marrow (left), yellow marrow (center) and bone marrow infiltrated with Gaucher cells (right).
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**Bone marrow- MRI**

In adult long bones, fat is the predominant contributor to the bone marrow signal pattern on MR images [14,15]. Both on T1-weighted spin echo sequences as well as fast spin echo T2-weighted sequences the signal from fatty marrow is optimized. Especially on T1-weighted images the contrast between fatty marrow and red marrow as well as most pathological processes is enhanced. When general marrow screening is performed, the primary anatomic sites for evaluation are the spine, particularly the lumbar spine due to the larger vertebral bodies, and the pelvis and proximal femurs. Since these areas contain a large percentage of red marrow throughout life it is logical to focus on these areas.

Typical signal patterns on T1-weighted images of yellow marrow roughly is similar to the subcutaneous fat [14,16,17]. Normal red cellular marrow is hypo-intense to yellow marrow on T1-weighted images. On fast spin echo T2-weighted sequences both fat and water will show high signal intensity [14,16,17].

**Bone marrow- Gaucher disease- MRI**

In Gaucher disease the normal marrow contains is replaced by glucocerebroside-loaded macrophages, Gaucher cells, leading to a lowering of signal intensities both on T1- and T2-weighted images [18-21]. The marked shortening of the T2 relaxation time appears to be the principal cause. This effect differs from most other diseases in bone marrow, in which a high signal intensity on T2-weighted sequences is encountered [22]. The bright signal that arises from normal bone marrow fat on T1-weighted images contrasts strongly with weak signal from Gaucher tissue and thus the T1-weighted sequences are most useful in assessing the extent of disease. In Gaucher disease both homogeneous and heterogeneous patterns of involvement are encountered [23]. Marrow involvement generally follows the distribution of red cellular marrow in Gaucher disease, progressing from axial to peripheral and in a long bone from proximal to distal with a tendency to spare epiphysis and apophysis [19,24,25].

In order to quantify bone marrow changes in Gaucher disease Quantitative Chemical Shift Imaging (QCSI) was explored [26].
This technique, described in more detail in one of the next paragraphs of the introduction of this thesis, was evaluated in hematological bone marrow disorders by the group from Massachusetts General Hospital [27]. They investigated the use of QCSI in healthy volunteers, patients with leukemia or aplastic anemia. It was shown that the fat-fraction, measured by this QCSI technique, was the single best discriminator between the groups. The change in fat-fraction was found to represent the underlying reason for many of the changes observed in conventional MRI. The same research group also explored the use of this technique to quantify longitudinal changes in bone marrow that occur during induction chemotherapy in patients with acute leukemia [28]. Results were correlated with bone marrow biopsy results. QCSI data showed sequential increase in fat-fractions among responding patients, consistent with biopsy-confirmed clinical remission. It was concluded that QCSI proved useful in assessing treatment response in acute leukemia during early bone marrow regeneration and later in ascertaining remission or relapse. Furthermore, an additional described benefit of QCSI was the ability to sample a large portion of bone marrow.

The same group tested the QCSI technique in vertebral bone marrow in patients with Gaucher disease [26]. The measured fat-fractions were correlated with quantitative analysis of marrow triglycerides and glucocerebrosides. An MR spectroscopy performed in these surgical marrow specimens showed a single fat and water peak, thus validating use of QCSI. Glucocerebroside concentrations were higher in Gaucher marrow and inversely correlated with triglyceride concentrations. It was concluded that QCSI is a sensitive non-invasive technique for evaluating bone marrow infiltration in Gaucher disease, showing great promise as a non-invasive method to monitor bone marrow response to treatment. In order to validate bone marrow response data acquired by QCSI an analysis of the lipids of normal and Gaucher bone marrow is performed [29]. In normal marrow triglycerides were by far the most abundant lipid (278 ± 70 mg/gm wet weight); the concentration of glucocerebroside in normal marrow was 0.061 ± 0.06 mg/gm wet weight. Gaucher marrow had dramatically lower triglyceride levels of 82% (51 ± 53 mg/gm wet weight) and as expected marked elevation of glucocerebroside (7.1 ± 3.4 mg/gm wet weight) [29]. It was concluded that these data support a model of bone marrow alteration in Gaucher disease in which triglyceride-rich adipocytes are progressively replaced by Gaucher cells, leading to an overall reduction in total lipid content.
This phenomenon is concluded to provide an explanation for the changes found in QCSI measurements in Gaucher patients [29].

**DIXON QUANTITATIVE CHEMICAL SHIFT IMAGING**

The MR-signal for a normal MR-image originates from two types of hydrogen nuclei: nuclei in water molecules and nuclei in fat molecules [30]. The two types of nuclei have a slightly different MR frequency, due to the so-called "chemical shift" effect. The Dixon method uses this frequency difference to separate the signals from water and fat, which makes it possible to quantify the fat signal fraction, $F_f$. Hence: Dixon quantitative chemical shift imaging (Dixon QCSI).

**Figure 2.** Localizer and Dixon acquisitions of the lumbar vertebrae L3, L4, and L5

**Figure 3.** From the phase difference between the Dixon acquisitions the sign image is deducted.
We apply this method to measure \( F \) in the lumbar vertebrae (L3, L4, and L5). As shown in Fig. 2, a coronal measurement slice (if necessary slightly tilted to transversal) is set out on a sagittal localizer image, such that the posterior part of the vertebrae of interest are optimally visualized (Fig. 2).

In the original Two-Point Dixon technique, which we use, two sets of acquisitions are performed [30]. One in which the water signal (W) and the fat signal (F) are "in-phase" (I), which means that at any moment in time, the fat and water spins point in the same direction, and their signals add up in the image: \( I = W + F \). In the second acquisition fat and water have opposed-phases (O): fat and water spins point in opposite directions, and the resulting image shows the magnitude of the difference of the fat and water signals: \( O = |W - F| \). (See Fig. 2).

**Figure 4.** Calculation of the water image.

In order to separate the water and fat signals we need to know in every pixel which signal is stronger. The phase-difference between the two acquisitions helps us to sort out regions with water dominant signal and regions with fat dominant signal. In the example of Figure 3, water dominant regions are grey in the phase-difference image, fat dominant regions are either white or black. A complication may be formed by inhomogeneities in the main magnetic field, which cause grey scale intensity variations across the phase-difference image. We developed an algorithm [31] that takes care of all these effects, and is able to produce from the phase-difference a sign image (S) (Fig. 3), which tells water dominant regions (white, \( S = +1 \)) from fat dominant regions (black, \( S = -1 \)).

With help of the sign image, water and fat images are obtained by simple
algebraic manipulations. For the water image (W) we have: $W = I + S \cdot O$ (Fig. 4), and for the fat image (F) we have: $F = I - S \cdot O$ (Fig. 5).

The last step is to compute $F_f$, again by elementary algebra, as shown in Figure 6: $F_f = \frac{F}{F + W}$. In order to easily read the $F_f$ values from the image, we display the $F_f$ image with a color scale: the color strip next to the image tells which color corresponds to which $F_f$ value from 0 (black) to 1 (white).

Figure 5. Calculation of the fat image.

Figure 6. Calculation of the fat-fraction and display of the fat-fraction with a color scale.
AIM AND OUTLINE OF THE CONDUCTED STUDIES

To evaluate the applicability and feasibility of Dixon QCSI as a technique to assess bone marrow invasion in our Dutch population of patients with Gaucher disease at first the technique was tested in healthy volunteers. In Chapter 2 the reproducibility of the Dixon QCSI technique in healthy volunteers as well as various operator dependent variables are tested. Furthermore, the results are compared to literature data. The differences are discussed.

In Chapter 3 an overview is given of the available imaging modalities at hand for the evaluation of skeletal involvement in Gaucher disease, both qualitative and quantitative. Various perspectives from different radiological groups in the world on this subject as well as an overview of the available literature is presented. In Chapter 4 the Dixon QCSI results are presented of the Dutch adult Gaucher disease population at baseline, without therapy. These fat-fraction data are related to clinical bone disease parameters such as presence of infarction, bone pain, bone crisis, avascular necrosis and joint replacement. The clinical relevance of the obtained fat-fraction number is illustrated.

In Chapter 5 the results of a study concerning Dixon QCSI as follow-up parameter for bone marrow response to enzyme supplementation therapy (EST) are described. Both treated and untreated patients are longitudinally evaluated. In Chapter 6 an overview is presented on the data available from various Gaucher treatment centers in Europe and one center in the USA as well as the Gaucher Registry Database concerning response of bone marrow to EST. A variety of modalities are used at the different centers to evaluate bone marrow response.

The need for widely available easy to use alternatives to Dixon QCSI for centers in which this technique is not present is obvious. In the next two chapters alternatives are tested against Dixon QCSI. In Chapter 7 a parameter is studied based on the ratio between signal intensity in a vertebral body and an intervertebral disc. This vertebral-disk ratio (VDR) is measured in patients without bone marrow disease and Gaucher disease. Furthermore, the VDR as parameter to detect response of bone marrow to EST is tested. Chapter 8 describes the study of another alternative for Dixon QCSI, namely the bone marrow burden score (BMB).
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Two observers test this score in patients with Gaucher disease without treatment against Dixon QCSI. Also the strength of BMB as response parameter is evaluated.

In Chapter 9 an overview of the results of these studies is given and the conclusions are discussed. Some areas for future research are described.

REFERENCES


Chapter 1


