Clinical applications of Dixon chemical shift MR imaging: Morbus Gaucher, Morbus Hansen
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Citation for published version (APA):
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Chapter 9

Summary, general discussion and future research
SUMMARY
In this thesis the experiences of a University Hospital, a national referral center for Gaucher disease, in analyzing bone marrow involvement in Gaucher disease are described. After it became clear that the organomegaly and cytopenia improved upon treatment with enzyme supplementation therapy (EST), bone disease became the most important clinical issue to address. Bone disease in Gaucher disease involves two, different structures: bone structure, that is distorted and bone marrow, that is infiltrated. It is thought that the progressive infiltration of bone marrow with Gaucher macrophages eventually leads to structural bone changes. These changes may develop into areas of infarction or avascular necrosis and in the end stage into arthroplasty. For patient management this difference is important, since these structural bone changes will show a different response rate to therapy when compared to bone marrow infiltration. The apparent slow response of the osseous involvement in Gaucher disease, when measuring structural bone changes, is most likely not a good indicator for assessing bone marrow response on EST. A technique that directly evaluates the changes in bone marrow can be expected to provide more valuable information on response to therapy. Dixon quantitative chemical shift imaging (Dixon QCSI) has been described as a quantitative imaging technique of bone marrow [1-3]. This technique can be used to measure the degree of Gaucher cell infiltration in the bone marrow by detecting decrease in fat (triglyceride) fraction. The strength, limitations, value and alternatives of this DQCSI technique in Gaucher disease were explored in this thesis.

The first three chapters concern the present approaches towards imaging of skeletal disease in untreated patients with Gaucher disease, with a special focus on Dixon QCSI. Dixon QCSI is a non-standard sequence on MRI-scanners and initial research at our institution concerned implementation of the technique with evaluation of reproducibility.

In Chapter 2 we describe a study in which the reproducibility of the Dixon QCSI technique was explored in measuring fat-fraction ($F_f$) in the lumbar spine (vertebrae L3, L4, and L5) in 16 adult healthy volunteers. We measured $F_f$ in the same volunteer on different days. Furthermore, we evaluated the influence on the reproducibility of two operator-dependent
aspects, namely (re-)positioning of the measurement slice and determination of the contours from which the regions of interest (ROIs) were calculated.

The mean $F_j$ was 0.37 (SD 0.08). The SD due to repeated measurement on different days was small, and mainly explained by slice (re-)positioning. No significant difference was found in $F_j$ between the different levels (L3-L5). Also no differences were found in contour drawing between two operators. We concluded that the Dixon QCSI technique is a powerful non-invasive tool in evaluating bone marrow composition; when used to evaluate the same person longitudinally it had an excellent reproducibility. We therefore recommended its use in protocols concerning axial (red) bone marrow involvement or marrow characterization.

In Chapter 3 an overview is given on the various radiological modalities that are available for imaging and quantifying skeletal involvement in Europe and the United States of America. This chapter is a reflection of a round table discussion that took place in Trieste (Italy) in April 2001. In this expert meeting a number of presentations were given concerning the various modalities that were used at various sites in the world concerning skeletal involvement in patients with Gaucher disease. There was a remarkable variation due to practical considerations such as availability and cost. However, concerning applicability it was concluded that magnetic resonance imaging (MRI) is the imaging technique of choice to evaluate bone marrow invasion as well as skeletal complications. Plain radiographs and computed tomography (CT) cannot play a significant role and therefore should not be used to assess bone marrow invasion. However, at which site of involvement the MRI should focus on remains a debate. Both the American group of Terk as well as the German group of Poll focuses on the peripheral bone marrow [4-6]. This is in contrast with the literature from the group from Boston [1-3,7-9] who focuses on the axial bone marrow being the site of involved in all known cases. The Dutch working group on Gaucher disease followed this concept, supported by the literature data on hematological malignancies that describes spread of disease through a centrifugal path of distribution [10]. The axial bone marrow is in this concept the first site of involvement. The main disadvantage of conventional MRI is the fact that it is not
quantitative. It was concluded that Dixon QCSI might be the most sensitive technique to quantify bone marrow invasion, yet an important drawback is the limited availability.

In Chapter 4 an attempt is made to correlate the fat-fraction $F_f$ as measured by Dixon QCSI to clinical relevant endpoints for bone disease, being the presence of chronic bone pain, bone crisis, avascular necrosis, pathological fractures and the need for surgical intervention such as joint replacement. We evaluated the $F_f$ in 30 untreated adult patients with Gaucher disease and related this to the $F_f$ of healthy volunteers. Furthermore, we studied the relation of $F_f$ with presence, absence and severity of the previously mentioned bone disease parameters. The $F_f$ in Gaucher disease patients ranged from 0.08-0.40 and was significantly lower than in the healthy population (0.27-0.55, $p<0.001$). Bone complications primarily occurred in patients with an $F_f<0.23$ and univariate logistic regression analysis indicated that for every decrease of $F_f$ of 0.1 the risk of bone complications increased with 85%. It was concluded that the $F_f$ of the lumbar spine measured with Dixon QCSI is associated with the occurrence of bone complications and may therefore be a clinical useful parameter. However, only a longitudinal study in patients under therapy can prove its value in clinical decision-making and outcome. Patients with Gaucher disease should be monitored for skeletal involvement on a regular basis and Dixon QCSI seems appropriate for this purpose.

The next two chapters focus on the role of imaging in evaluation of the response of bone and bone marrow disease in patients with Gaucher disease with a special attention to Dixon QCSI.

In Chapter 5 the results of Dixon QCSI as response parameter to individualized doses of enzyme supplementation therapy (EST) in Gaucher disease are described. In 12 adult Gaucher disease patients and in 9 untreated Gaucher controls, fat-fractions ($F_f$) were measured prior to and during EST. During treatment $F_f$ increased significantly already after 1 year in 11/12 patients. After 4-5 years $F_f$ normalized in 11/12 patients, but remained low in the untreated Gaucher controls. When the fat-fractions of healthy volunteers are taken into account (Chapter 2), one may conclude that Dixon QCSI is a sensitive tool for measuring bone
marrow response to EST already after one year. It seems the modality of choice for the assessment of bone marrow response to EST and therefore should be included in annual follow-up of treated patients with Gaucher disease.

**Chapter 6** is a reflection of a second round table discussion session held in Trieste in April 2001 on the response of Gaucher bone disease to enzyme therapy. From various centers in Europe as well as the USA data were discussed concerning the regional protocols for evaluating bone and bone marrow disease and its response to enzyme therapy. There was a wide variety of imaging protocols, with no similar protocol in any of the centers. Participants concluded that quantification is the method of choice for evaluation of the response on EST, and that every group of clinicians treating Gaucher patients has its own quantitative method of choice. Some will focus on peripheral bone marrow, others - like the Dutch working group on Gaucher disease - focus on axial bone marrow. It is thought that response of bone marrow compartment may occur as soon as the response of the visceral compartment.

Dixon QCSI is a powerful technique detecting response of bone marrow to enzyme supplementation therapy (EST) as early as after one year. However, the technique is not widely available. Therefore efforts were made to study more widespread available alternatives for Dixon QCSI, evaluating axial bone marrow. **Chapters 7 and 8** focus on potential alternatives for Dixon QCSI. In **Chapter 7** the Vertebra-Disc Ratio (VDR) is described as alternative to Dixon QCSI. The ratio of the gray value on T1-weighted images of the vertebral corpus L3 and the healthy intervertebral disc L3-L4 was determined in controls as well as treated and untreated Gaucher disease patients. The normal VDR was $1.9 \pm 0.3$ and differed significantly from both untreated and long treated Gaucher disease patients. The VDR is concluded a useful parameter with a good correlation with the fat-fraction. In **Chapter 8** another alternative is explored. The Bone Marrow Burden score (BMB) is the first semi-quantitative scoring system in which both the axial and peripheral bone marrow is included. In 30 Gaucher disease patients the BMB was scored by two radiologists unfamiliar to Gaucher disease. A good and significant correlation was found between the two observers, a very good intra observer variation was shown and a good and significant correlation
with Dixon QCSI was found. The detection of response to EST was present, yet less than with Dixon QCSI. Of the two components, axial lumbar spine bone marrow showed more response than peripheral femur bone marrow. BMB was concluded to be a good reproducible easy to use scoring system that can serve as alternative for Dixon QCSI, when not available.

**GENERAL DISCUSSION AND FUTURE RESEARCH**

The studies included in this thesis demonstrate the feasibility and clinical relevance of quantitative MR imaging with use of the Dixon QCSI technique in Gaucher patients. It showed to be a very sensitive reproducible technique that is related to clinical important features as bone complications and it detects response to therapy already after one year of treatment. In our clinical management of patients it plays an important role.

This thesis also enlightened on a limitation of the technique, namely the unavailability worldwide. Another drawback of the technique is the manual handling of the data sets. The program to acquire fat-fraction numbers from the acquired data needs a physicist's intervention. It would be beneficial when this process can be computerized in the near future.

At our institution two possible alternatives to analyze bone marrow involvement in Gaucher disease were studied; VDR and BMB. Both techniques are easy to use as standard MRI hardware and software suffices. Both techniques have been correlated with Dixon QCSI, and have been shown to detect response to EST. So which one is the best to choose? This question, though very legitimate cannot be answered by our results, since our follow-up data numbers are small. So, only a hypothetical discussion is possible. An advantage of the VDR might be the fact that a pure quantitative measurement is produced, avoiding interpretation bias produced by observers. Furthermore, this technique can be carried out on every commercially available MR machine, without the aid of a physicist. However, the inclusion of the intervertebral disc as part of a bone marrow scoring system introduces a variable that is under the influence of external factors, like age or diurnal variation [11-13]. When focusing on BMB, a strong feature of BMB might be the inclusion of both axial and peripheral bone marrow. Although our BMB results show better response detection in the lumbar spine component of BMB, in a
small number of patients a better response is detected in the peripheral femoral bone marrow. Furthermore, the fact that areas known to be at risk for developing avascular necrosis, i.e. femoral epiphysis, are included in an annual evaluation of the individual Gaucher disease patient will reassure treating clinicians. To compare the alternatives more data are necessary. For this purpose the bone marrow data throughout the world, acquired by MRI, might be assessed at a central research center. Digital MRI datasets, when stored, can be assessed for both VDR and BMB. Patients from various sites could be enrolled in a single database, from which better statistical analysis can be performed.

Another alternative for coping with the limited availability of Dixon QCSI would be to increase the availability of Dixon QCSI. Theoretically it would be possible for the pharmaceutical companies to provide the service of having a small group of physicists experienced with Dixon QCSI available for implementation and training purposes. In this way in every country a center where patients with Gaucher disease may have their annual fat-fraction measurement taken is present.

The group that is difficult to analyze with Dixon QCSI is the group of children and adolescents with Gaucher disease. In this group the amount of cellular marrow present in the axial marrow varies with age, making the measurement of fat-fractions difficult to interpret; red cellular marrow will show a low fat-fraction, which cannot be differentiated from Gaucher cell infiltration. It would be of great value to enroll children and adolescents without bone marrow disorders in a Dixon QCSI database. In this way age-matched controls are present and the evaluation of the fat-fraction obtained in young Gaucher patients (children and adolescents) could be improved. However, the practical arrangements for such a database acquisition are cumbersome.

By evaluating three lumbar spine levels with non-invasive Dixon QCSI, a large amount of axial bone marrow is analyzed. The chance of occurrence of sampling errors is minimized. Therefore, this technique is potentially powerful in the exploration and characterization of various bone marrow disorders and their response to therapy. In collaboration with the department of hematology we are planning to evaluate patients undergoing bone marrow transplants in this manner. It might be possible
to detect early response to transplantation in a non-invasive manner prior to the changes that can be found in the peripheral blood and provide us with prognostic parameters, without bone marrow sampling error [14-21]. The non-invasive capability of bone marrow characterization is a very important feature of Dixon QCSI. Especially, the use of this technique in a pediatric population of patients with bone marrow disorders is tempting. To be able to characterize bone marrow alterations due to various diseases and its response to therapy in a non-invasive manner would be of great benefit to the pediatric patient. Since in evaluating the response to therapy, the patient is its own control, the need for a data base of healthy volunteers in various age groups would not be obligatory, however desirable.

Although the value of Dixon QCSI is explored in detail in an adult population with Gaucher disease, as presented in this thesis, the possibilities for further research are present and stimulating. The exploration will continue.

REFERENCES

Summary, general discussion and future research
