

SUCCESSFUL AND UNCOMPLICATED TRANSFER OF MRI QUANTITATIVE CHEMICAL SHIFT IMAGING (QCSI) TECHNOLOGY FOR THE DETECTION OF BONE MARROW FAT SIGNAL FRACTION IN TYPE I GAUCHER DISEASE

A. Vanclooster¹, W. Meersseman¹, M. Maas², S. Ghysels³, R. Peeters³, E.M. Akkerman²,
D. Cassiman¹

¹*Metabolic Centre, University Hospital Leuven, Gasthuisberg, Belgium*

²*Academic Medical Centre Amsterdam, the Netherlands*

³*Department of radiology, University Hospital Leuven, Gasthuisberg, Belgium*

Correspondence to:

Annick Vanclooster
Department of Pediatrics and Metabolic Center
University Hospital Gasthuisberg
University of Leuven
Herestraat 49, 3000 Leuven
Belgium
Tel: +32-16-348472
Fax: +32-16-343842
Email: annick.vanclooster@uzleuven.be

David Cassiman: david.cassiman@med.kuleuven.be
Wouter Meersseman: wouter.meersseman@uzleuven.be
Stefan Ghysels: stefan.ghysels@uzleuven.be
Ronald Peeters: Ronald.peeters@uzleuven.be
Mario Maas: m.maas@amc.uva.nl
Erik Akkerman: e.m.akkerman@amc.uva.nl

ABSTRACT

Background and study aim: Dixon Quantitative Chemical Shift Imaging (QCSI) to measure lumbar spine bone marrow fat signal fraction (FF), is considered the ‘gold standard’ for the determination and follow up of bone involvement in type I Gaucher disease (GD). Since there used to be only one centre in Europe (AMC, Amsterdam, the Netherlands) offering this technique, we transferred the Amsterdam QCSI technology to the University Hospital Gasthuisberg (Leuven, Belgium) and tested it on 9 Belgian patients.

Patients and methods: 9 GD patients entered the study from November 2006 till April 2010. Installation of the QCSI technique in Leuven required a visit of the Amsterdam MRI physicist (E.M.A.) for one day, to install software and train the local team. Requirements for running the technique are: a 1.5 Tesla MRI-scanner, Siemens or General Electric, with access to sequence programming and a dedicated physicist. A total of 22 scans were performed in Leuven and in 2 patients parallel scans were performed at the AMC, to determine reproducibility. The critical cut-off value of FF for bone disease is 23%, according to data published by the Amsterdam group.

Results: Four patients were scanned once and five patients at least 3 times. Two parallel scans in Leuven and Amsterdam were each performed within one week and showed good reproducibility (40.7% vs. 43.8% and 41% vs. 39%). Due to a shortage of enzyme, enzyme replacement therapy ceased from August 2009 till January 2010, causing a detectable decrease in FF in 3 patients. This confirms that QCSI is useful in clinical follow-up.

Conclusion: This study shows that Dixon QCSI MRI technology is successfully transferable from one centre to another, offering the potential for spreading this technique to Gaucher MRI expert centres throughout the world.

Keywords: *QCSI (Quantitative Chemical Shift Imaging), Gaucher disease (GD), Imiglucerase, Enzyme Replacement Therapy*

BACKGROUND

Gaucher disease (GD) (OMIM +230800) is an inherited metabolic disorder (1), caused by a deficiency in the lysosomal enzyme glucocerebrosidase. It results in the accumulation of glucocerebroside in the macrophages throughout the body, especially in the bone marrow, liver and spleen. There are three subtypes of GD: type I, non-neuropathic, is characterized by hepatosplenomegaly, thrombocytopenia and painful bone crises. The acute neuropathic type II and subacute neuropathic type III classically start during infancy. Neurological symptoms predominate in these two types of GD, and they are usually lethal in the first decade (1; 2).

Since its beginning in 1992, enzyme replacement therapy (ERT) with imiglucerase has become the standard treatment for GD type 1. ERT stabilizes or reverses the disease manifestations: liver and spleen volumes decrease or stabilize, platelet counts and hemoglobin increase, bone disease diminishes and quality of life improves (3).

Follow-up of patients with GD consists of routine blood monitoring, radiological follow-up of liver and spleen volume, bone densitometry and magnetic resonance imaging (MRI) of bony structures. An important debilitating feature of GD type I is bone disease. About 80-90% of patients (at any age) have some degree of bone manifestations during their lifetime including distal femoral deformities (Erlenmeyer's flask deformities), lytic lesions, osteopenia, osteoporosis, bone pain and bone crises (2; 4). At the Massachusetts General Hospital, Boston as well as in the Netherlands, at the Academic Medical Center (AMC) in Amsterdam, Dixon Quantitative Chemical Shift Imaging (QCSI) was validated as a

parameter of bone marrow involvement in type I GD (4; 5; 6; 7). QCSI provides quantitative information by separating the individual contribution of water signal and fat signal in bone, from which the fat signal fraction (FF) is calculated. The lumbar spine, L3 – L5, is the preferred location for the assessment of FF. A decreased FF is caused by the infiltration of Gaucher cells in the bone marrow and is correlated with the risk of bone complications (4; 7). In the healthy population, FF values range from 27% to 55% (mean 37%). Maas et al. (2002) reported an increased frequency of clinical bone complications in patients with a FF of less than 23%. Univariate analysis showed that an increase of 10% in FF corresponded to a decrease in the relative risk for developing bone complications by 85%. The eligibility for ERT can be evaluated with QCSI and ERT dosing adjustments can be monitored with QCSI (4; 8).

New measurement techniques and methods often end up being performed in one centre only. As we considered the QCSI technique a powerful addition for the clinical follow-up of GD patients, we thought it would be worthwhile to have it installed in GD centers worldwide. To this end, we wanted to test if the technology could be transferred from Amsterdam to another tertiary academic center.

MATERIALS AND METHODS

Study population

Between November 2006 and April 2010, 9 patients (3 females, 6 males) with GD type 1, were scanned at the University Hospital Leuven. The diagnosis was based on genotyping and/or deficient glucocerebrosidase activity in leucocytes in all patients. The presence of bone complications was not mandatory. The

following parameters were recorded: history of bone crises, chitotriosidase levels (as marker of macrophage activation) and data on treatment with imiglucerase.

Furthermore three normal controls were scanned and two patients had a scan in Leuven and Amsterdam within 1 week. Data of healthy volunteers (7; 8) were used to define normal values.

The study was approved by the local Ethics Committee and written informed consent was given by all participants.

Dixon QCSI

A Dixon QCSI scan was performed to analyze the FF in the lumbar bone marrow of L3, L4 and L5. We applied the same technique as has been used in Amsterdam (4). Requirements for running the technique are: presence of a local physicist, a 1.5 Tesla MRI scanner, Siemens or General Electric, with access to sequence programming. In-phase and opposed-phase proton density weighted SE sequences were performed with the

following parameters: TR/TE, 2500/22; slice thickness, 4 mm; matrix 256 x 256; number of excitations, 1; field of view, 350 x 350 mm². As described in (8) (para-)coronal measurement acquisition slices were positioned on a midsagittal localizer image, passing through the middle of the posterior parts of L3, L4 and L5, this to avoid motion artifacts, FF was determined on a pixel by pixel basis, and regions of interest in L3, L4 and L5 were derived. Reported FF values are the average of the three regions of interest. Postprocessing and data analysis were performed on a Sun Sparc 20-51 workstation (Sun Microsystems, Mountain view, CA).

RESULTS AND DISCUSSION

The study was started with three healthy controls. All had a normal FF (table A). Nine patients were included in the study (age range 30-71 years, mean 50), two of which were scanned at the University Hospital Leuven, Gasthuisberg and at the AMC in Amsterdam in the same week (table B).

Table A: Dixon QCSI results (%) of control patients in Leuven

Control patient	Result
1	31
2	36.5
3	39.2

Table B: Dixon QCSI results (%) of patients in Leuven

Patient	2006	2007	2008	2009	2010	2010(AMC)
1					40,7	43,7
2	43,2		43,6		41	39
3	24,4		27,5		29,8	
4	30,6			26,7	24,1	
5		40,8	39,9	35,1	31,8	
6		44				
7		32,5				
8		61,2				
9		41,2				

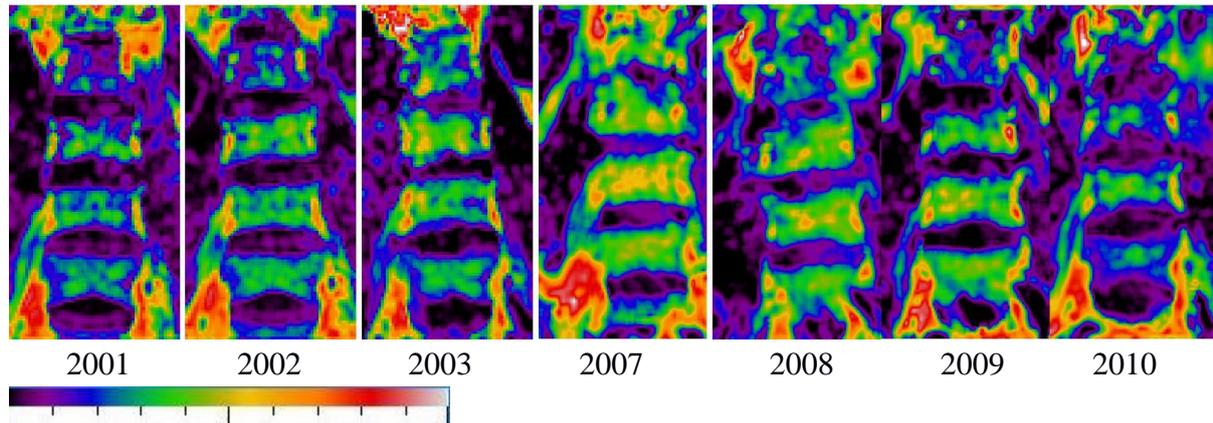
Patient results

Patient 1 is a 71 year old man who never received ERT, but did suffer an avascular necrosis of the left hip. The scans in Leuven and Amsterdam showed a FF of respectively 40,7% and 43,7%. Patient 2, a 52 years old female patient, received imiglucerase for over 13 years. In August 2010 she stopped therapy for over 10 months as a result of production problems. The FF in April 2010 was 41% in Leuven and 39% in Amsterdam. The cause of minor differences in FF is the occurrence of small differences in the patients' position and the demarcation of regions of interest on the vertebrae. In 1991, patient 3, a 52 year old man, received intra-articular steroid injections into the left hip, for what most probably also was an avascular necrosis. He ultimately underwent a hip replacement in 1995. Although he never received ERT, his FF increases over the years. In 2006, his FF was 24,4% and now in 2010 he has a FF of 29,8%. Patient 4, a 30 year old male patient, started with a FF of 30,6% and now, four years later, his FF has gradually decreased to 24,1%. He started ERT in 2004 and stopped for over six months in

August 2010 as a result of stock problems with imiglucerase (table B). Although his compliance has been poor over the last six years, he never had any signs of bone crises so far. The bone densitometry shows mild osteopenia. Patient 5, a 37 year old woman, was diagnosed with GD at the age of 12. She started with imiglucerase in 2001. At that time, she had a FF of 29% while receiving imiglucerase 30U/kg every other week. In the first three years (2001 – 2002 – 2003) her FF was measured in AMC, Amsterdam. Her chitotriosidase levels were out of normal range during three years. In 2007, the dose of imiglucerase was increased to 60 U/kg fortnightly because of an avascular necrosis of the left hip. Due to the dose change, her chitotriosidase levels normalised and the FF increased to 40.8%. After one year, the dose was decreased to 30U/kg every other week till August 2009 as a result of lack of imiglucerase. During this period, the chitotriosidase levels remained stable. In January 2010, after receiving no therapy for over six months, chitotriosidase levels were above normal again, her FF decreasing by 9% compared to three years earlier (table C; figure A).

Table C: Results of patient 5

Patient 5	2001	2002	2003	2007	2008	2009	2010
QCSI (%)	29	33	35	40.8	40	35	31.8
Chitotriosidase levels	2131	1471	1044	28.9	22.45	18.39	54.99
ERT (U/kg/2w)	30	30	30	60	60	30 (till August)	15 (from January on)

Figure A: Evolution of the fat fraction in patient 5

Patient 6 to 9 were scanned once. They were referred from other centers. Three of these patients had normal values (27% - 55%; mean 37%). One patient, patient 3, showed a high FF of 61,2%. Unfortunately, due to lacking clinical data, we were unable to correlate these results.

CONCLUSION

This study shows that Dixon QCSI MRI technology is easily transferable from one centre to another. This offers the potential for spreading this technique to Gaucher MRI expert centres throughout the world and would allow Dixon QCSI to become a generalised method to evaluate Gaucher patients. The results of the FF measurements can aid in clinical decision-making concerning ERT initiation, monitoring and dose adjustments, as we illustrate here by showing decreasing FF in patients after cessation of enzyme therapy.

LIST OF ABBREVIATIONS

QCSI: Quantitative Chemical Shift Imaging
 GD: Gaucher Disease
 AMC: Academic Medical Centre
 ERT: Enzyme Replacement Therapy
 FF: Fat Fraction

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

AV, DC, WM, RP and SG were involved in the clinical follow-up of the patients, the data analysis and interpretation and drafted the manuscript. EMA and MM performed the scans in the Netherlands of three patients. All authors read and approved the final manuscript.

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LEGEND

Table A: Dixon QCSI results (%) of control patients in Leuven Table B: Dixon QCSI results (%) of patients in Leuven

Table C: Results of patient 5

Chitotriosidase levels of 2001, 2002 and 2003 were expressed in nmol/h/ml and normal range is 4 – 195. 2007 – 2010 are expressed in $\mu\text{mol/L/h}$ and normal range is 0.06 – 38.

Figure A shows the evolution of the fat fraction in patient 5 in lumbar vertebrae L3, L4 and L5. Fat is depicted as a color range (from purple, over blue, green, yellow and orange to red). The more yellow, orange and certainly red are seen in the vertebrae, the more fat is present. Results of FF measurements can be seen in Table 3.