

Ph.D. Theses

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Diagnostic value of imaging methods in Gaucher's disease

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## 1. Introduction, aims:

Gaucher disease (GD) is an autosomal recessively inherited lipid storage disease caused by the accumulation of glucolipid stored in the lysosomes of macrophages. We seldom come across it in everyday life, however, it is the most frequent one among storage diseases. Three types of GD is known and out of them 99% belong to type 1 GD. One of the leading symptoms is splenomegaly, as a result of which the abdomen protuberates. The size of spleen might increase a hundredfold (!) of the original one. In most cases splenomegaly is accompanied by hypersplenism (thrombocytopenia, anemia, leukopenia). Hepatomegaly is also characteristic; generally the volume of the liver increases to sesquialter or double of the original volume. Among the storage diseases it is the GD that affects most frequently the bone marrow and bone system within which the femur is affected almost 100%. Bone changes are varying from moderate osteopenia to severe destruction of bone resulting the complete destruction of joint. Gaucher cells might also infiltrate the wall of alveoles of the lung, small vessels, alveolar area and mediastinal lymph nodes.

Until the late 80's the treatment of GD had focused only on mitigating the symptoms and pain. In cases of significant pancytopenia and hypersplenism the spleen had also been removed. Frequently, it was necessary to implant endoprotheses due to degenerative bone and joint processes, however, the greater threat of infection and bleeding has increased the risk of operation. The recognition of mannose receptors of macrophages has provided the possibility for the immission of the enzyme into the lysosomes and thus the enzyme replacement therapy (ERT) could have started in 1991. Initially alglucerase (Ceredase®) made of human placenta was used, recently imiglucerase (Cerezyme®) produced by recombinant technology is used worldwide. The result of bone-marrow transplantation is uncertain in case of GD disease; therefore even earlier it had been applied only in acute cases. In principle the possibility of gene therapy is given, however, the attempts hitherto did not produce results therefore the continuous enzyme substitution therapy can be regarded as the basic therapy today and in the near future.

Several imaging methods had been applied in the diagnostics of GD disease focusing mainly on the organs in the upper part of the abdomen and on the bones and bone marrow since these are the most frequently affected organs. The introduction of ERT as a therapeutic procedure highlighted the importance of this issue since the measurement of the impact of this therapy has become one of the major goals.

Few publications in the domestic literature – except the last one-two years – deals with patients suffering from Gaucher's disease and even these publications contain only case histories. In my theses I should like to give an account of our comprehensive experiences gained in the course of abdomen and bone MRI examination and in the course of analysing conventional X-ray films and HRCT examinations of the lung of patients with GD receiving ERT and non-treated patients in Hungary. My aims were the following:

1. I have included 16 patients registered in the Hungarian Gaucher-Registry into my study who –following the medical check-up– regularly participated in the control examinations as well. I defined the volume of liver and spleen of the patients and examined the possible focal changes in the organs of the abdomen and the possibility of their differentiation by MRI examinations. In the case of one patient I was able to compare the MRI images of focal anomalies of the spleen with the pictures of macroscopic and histological examinations. I examined bone and bone marrow changes taken on the femora by MRI and correlation among the demonstrated anomalies and those visible on the X-ray film. I was looking for the answer to the question whether it is possible to indirectly deduct the severity of bone marrow infiltration from what is visible on conventional X-ray films. I examined the frequency of lung manifestation in patients and its characteristics on the HRCT images.
2. I was looking for an answer to the question whether the severity of liver and bone anomalies of splenectomized patients is different compared to that of the patients not operated on because there is no full agreement on this issue in the literature.
3. I have analysed the changes in the bones, bone marrow, liver and spleen as a result of ERT and the differences occurring in adults and children. I have examined the extent of the suitability of MRI examinations and conventional X-ray for follow-up.
4. I have examined in the course of control examinations the possible progression organs and bone changes of patients not receiving ERT.
5. In the case of suddenly developed pain localised to limbs, restricted mobility and fever I looked for signs by analysing MRI pictures and X-ray films that would serve as basis for deciding whether bone crisis or osteomyelitis is in the background, because this is fundamentally important from the aspect of the treatment of the patient.
6. The ERT of three patients has discontinued due to different reasons. I have examined the possible impact of ERT cessation on the liver, spleen and bones.

## 2. Patients and methods:

The Department of Infectology and Pediatric Immunology of Medical and Health Science Center, University of Debrecen directs the care and treatment of patients with GD in Hungary. Radiological examinations were performed and evaluated at the Department of Radiology. Sixteen patients (9 women, 7 men) out of 26 patients with GD certified by biochemical examinations had taken part in the examination and the annual control examinations until 2001. MRI examinations were performed since 1992; conventional X-ray films had been taken since 1989. On the date of the first MRI examination the average age of involved patients had been 21 years (4-65 years of age).

Before 1994 MRI examinations had been performed annually on the abdomen and femora by 0,5T field intensity Elscint Gyrex V type and from 1994 by 1T field intensity Shimadzu SMT 100X type MR equipment. Conventional X-ray had been taken on femora, spine and hip. In case of acute bone pain we made MRI and X-ray examinations on the painful limb within a few days. In one case we made CT examination from the left hip.

Nine patients received ERT. They were given alglucerase (Cerezyme®, Genzyme Therapeutics, Cambridge, MA, USA) between 1994-99 and since 1999 they are given imiglucerase (Cerezyme®, Genzyme Therapeutics, Cambridge, MA, USA) biweekly by infusion. The therapeutic dose was generally 30 IU/bwkg/month. In some cases (bone crisis, deterioration of laboratory parameters, increase of the size of liver and/or spleen) it was necessary to increase the dose of enzyme to 40-90 IU/bwkg/month.

### 2.1. Abdominal MRI examination:

We made abdominal MRI examination by applying body coil. We made axial T1 weighted (TR:500msec, TE: 20 msec), T2 weighted (TR: 2000 msec, TE: 90 msec) proton density (TR: 2000 msec, TE: 20 msec) and coronal T1 weighted (TR: 500 msec, TE: 20 msec) images by applying 1 cm slice thickness. The matrix was 256x256, and the FOV 40-45 cm. Volume of the liver and spleen were calculated at the first examination and its development later in the case of patients receiving ERT and of patients not receiving this treatment. In addition we described the focal anomalies visible in the liver or spleen and examined their changes during the control examinations. It was also our aim to judge the other organs of the examined region i.e. the pancreas, kidneys, adrenal glands and lymph nodes. We examined the impact, if any, of the cessation of ERT on the liver and spleen.

### 2.2. MRI examination of the femora

We made coronal T1w (TR: 500-600 msec, TE: 20 msec), T2 w (TR:2000-3000 msec, TE: 90 msec) and fat-suppressed STIR Short Tau Inversion Recovery, TR: 2000 msec, TE: 35 msec, TI: 110 msec) images from the femora by 4-5 mm slice thickness parallel with the run-off of thigh bone. The matrix was 256x256 and the FOV was 40-45 cm. We examined the signal intensity of bone marrow on the MRI pictures and evaluated the decrease of T1 and T2 signal as an indication of infiltration. Modifying the Rosenthal scale we have applied 6-point scoring system that makes the semi-quantitative measurement of Gaucher infiltration of femora. On this basis 0. stadium indicates the

lack of infiltration, while 1. indicates the infiltration of proximal metaphysis, 2. the diaphysis, 3. the distal metaphysis, 4. the trochanter major, 5. the trochanter minor and 6. the distal epiphysis. The scoring system takes into account that the bone marrow infiltration progresses from the proximal regions to the distal and the infiltration of epiphyses takes place last. The high signal visible on T2 and STIR images and the low signal detectable on T1 weighted images is characteristic of oedema and we evaluated this as a characteristic of the activity of the disease. The high signal on both the T1 and T2 weighted images is characteristic of the presence of extracellular methemoglobin thus it indicates hemorrhage. We examined the changes in the bones, the anomalies indicating fracture, chronic infarct or bone necrosis.

We have categorized the patients in 4 groups (normal, moderate, medium and serious grades) in accordance with the extent of Erlenmeyer-flask deformity visible on the conventional X-ray images taken on the thighbone. We also described the other bone changes visible in the femora and on this basis we have categorized the stadiums (0 = normal picture; 1 = expansion of medulla, osteopenia; 2 = circumscribed lysis, small cortical destruction; 3 = ischaemic necrosis, osteitis, sclerosis, diffuse destruction, osteoarthritis). We have given the combined compact width in *mm* (bone diameter minus medulla width) in the femur diaphysis of patients older than ten years of age. We evaluated the correlation – if any - between the diameter of compacta, the Erlenmeyer-flask deformity, the seriousness of bone deformations and the extent of bone marrow infiltration. We have separately examined the types of serious bone deformations in splenectomized patients. We monitored the change of the extent of bone marrow infiltration, the development of bone deformations in the patients receiving ERT.

We performed lung HRCT examination of 11 patients (Siemens Medical Systems, Erlangen, Somatom DR and Plus 4 CT equipment). 11 axial images in 1 mm slice thickness were made without adding intravenous contrast media, by applying 120 kV voltage and by special high frequency reconstruction algorithm.

We recorded the numerical data in Microsoft Windows Excel program. We used the Statistics for Windows program for recording the parametric data for evaluating the changes in the volume of liver and spleen. We accepted the  $p \leq 0,05$  value as significant.

### 3. Results and discussion:

1. I detected hepatomegaly in 81% of patients with GD (13 cases) and splenomegaly in the case of every non splenectomized patient. Considering its normal size the liver enlarged by 20-444% (by an average of 108,6%). The extent of splenomegaly was 9-52 cm<sup>3</sup> (25,14 cm<sup>3</sup>/ttkg) i.e. between 125-1200%. We did not find pathologic changes in kidneys, adrenals and pancreas. The spleen of one patient had been removed thus the histological analysis of focal changes visible on MRI became possible as well. The low T2 signal intensity focal changes correspond to the sheets of Gaucher cells, the high signal focuses beside the cells also contain enlarged sinusoids, but malignancy has not been proved. This confirms that focal change with high T2 signal is in most cases Gaucheroma, i. e. benign focus.

In all cases –with the exception of one patient– bone marrow infiltration could be found in the femora. It was not possible to establish the extent of infiltration on the basis osteopenia, Erlenmeyer-flask deformity, the compacta width or other anomalies of the bone visible on conventional X-ray films. Since X-ray films do not provide information on the extent of bone marrow infiltration, the severity of the disease might be underestimated therefore in the case of patients with GD MRI examination always has to be performed. If serious extent of infiltration can be seen on this, then ERT has to be started in order to prevent possible serious bone complications later. I did not find correlation between the size of liver or spleen and the severity of marrow infiltration.

It can be established on the basis of lung HRCT examinations that few patient are affected; fibrotic signs indicating the manifestation of the basic process could be found in the case of two patients.

2. Compared to the other patients the enlargement of liver had been considerably marked in the case of three patients splenectomized in their childhood (164%, 224% and 444%). Pathologic fracture, bone destruction and bone crisis had occurred more frequently in their cases. We did not find this in the case of those patients who had been splenectomized in their adulthood; the extent of hepatomegaly and affected bone marrow was less. Therefore our data confirm that serious bone complications and enlargement of the liver might be expected in patients splenectomized in their childhood. The earlier they had splenectomy the sooner the serious bone complications might occur.
3. Following 14-96 months ERT the volume of the liver of the patients decreased significantly, by an average of 40,77% and the volume of spleen by 41,1%. The tempo of the decrease was more marked in the first years. The extent of the decrease of the volume of the liver was greater in the case of splenectomized patients than in the case of non splenectomized patients. Focal changes appeared in the spleen of two patients and in one cases the already existing ones progressed and focal anomalies appeared in the liver of one patient.

Bone marrow infiltration has improved in seven out of nine cases that could be monitored well by our semiquantitative MRI examination method reducing the time of examination by half. Improvement can also be observed in splenectomized patients. The remodelling of the bones in the limbs of children can already be seen after 2-3 years treatment and this can be well demonstrated

by X-ray films. Substantial improvement cannot be seen on conventional X-ray films of the adults that might be explained by the slower turnover of bones in their case of adults.

The dependence of the affect on enzyme dose indicates that the dose of enzyme had to be reduced in the case of two patients due to financial reasons and after 1-2 years it has several times been followed by bone crisis. The symptoms quickly regressed by applying an increased quantity of enzyme. In the case of one patient the volume of liver and spleen first decreased during the treatment then progression has occurred. The size of visceral organs had again decreased as a result of applying increased dose of enzyme.

The volume of liver and spleen and its change due to treatment can be accurately defined by MRI. The procedure is sensitive in demonstrating bone marrow infiltration, and with its help it can be defined by semi-quantitative way; other bone pathology (with the exception of osteopenia, small lesions of compacta) and changes of soft tissues can also be demonstrated. The procedure is not harmful to health. On the basis of all these it can be established concordant with the international observations that MRI plays an important role in the indication of ERT, to define of the applicable dosage of enzyme and to define the effect of ERT.

4. In the course of control examinations there were no substantial changes in the abdominal organs of patients not receiving ERT. No deserving progress has occurred in the volume of liver and spleen. However, progress of bone anomalies had occurred in two cases where the bone marrow infiltration was serious. In one of these cases the patient had been splenectomized in his childhood and when he was 25 years old, bone destruction, aseptic necrosis, bone crisis developed. In the other case an old patient suffered pathological femur fracture. Our 10 years MRI follow up examinations indicate that in the case on non-treated adult patients substantial change in the visceral organs cannot be expected, but in case of serious bone marrow infiltration affecting also the epiphyses bone symptoms might deteriorate.
5. Within the period under review bone crisis occurred on four occasions in the case of two (splenectomized) patients receiving ERT and on two occasions in the case of two patients not receiving ERT. Conventional X-ray films and MRI examination has been performed as well of these patients. If high signal indicating blood subperiosteally or in the bone marrow was demonstrable on the MRI images, the diagnosis for the treatment could have been established in a non-invasive way. In the case of one patient biopsy was necessary and it confirmed the presence of pseudo-osteomyelitis. Therefore in the majority of cases MRI examination is sufficient for adequate diagnosis. However, X-ray films are not suitable for diagnosis, they have not shown anomalies only weeks-months after the appearance of symptoms, when complaints already eased or disappeared.
6. According to data published in literature the cessation of ERT does not cause problems in the case of adult patients; perhaps it leads to the slow deterioration of laboratory parameters but the case of one of our patients disagrees with this. This patient after a year has refused to continue the ERT due to psychosomatic

symptoms. In the following years the patient's condition has continuously deteriorated, extreme extent of the enlargement of liver and spleen and aggravation of bone marrow infiltration have occurred. Enzyme therapy has been restarted again after 4 years, but splenectomy had taken place due to the patient's hematuria. The pathological background of this rebound like event is not clear. It is possible that the lipid decomposition product created by the external enzyme impedes the gene coding the mutant glucocerebrosidase and thus it further reduces the already low internal enzyme activity. Whatever this mechanism might be, our unique observation suggests that in certain cases the cessation of ERT might lead to the rebound like progress of the disease.

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Impact factor of in extenso publications representing the basis of the theses: 11,417

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Aggregate impact factor of publications representing the basis of the theses: 18,892

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