

## Gaucher's Disease in Albanian Children: Casuistics and Treatment

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### Abstract

**Objective:** Gaucher's disease is a rare genetic disorder that results in the accumulation of cerebroside in the liver, spleen, kidneys, lungs, brain and bone marrow. The deficiency of the specific lysosomal enzyme glucocerebrosidase is considered as causative factor. The first effective treatment for the disease, the drug Ceredase, approved in 1995, was replaced in 2001 by the drug Cerezyme®.

**Methods:** During the period 2004-2009 in our service 11 children were hospitalized and treated for Gaucher's disease: 9 children with type 1, and 2 children with type 3 of the disease. The enzymatic examinations of the biomarker chitotriosidase were performed in Sahlgren's University Hospital, Mölndal Sweden; the DNA analysis was performed in the Children's Hospital & Regional Medical Center, Seattle, USA.

**Findings:** We are presenting the biological and genetic molecular data of the children. In our case series, one year after the treatment started, the hemoglobin level was normalized; the platelet count was normalized in 7 patients after one year of treatment, and in 9 patients after two years of treatment. The hemorrhagic syndrome stopped after 6 months of treatment. Chitotriosidase values decreased 10-20 times the initial value, after one year of treatment and in one case the value reached the normal range. The treatment with Cerezyme® has also improved the visceral and biological signs. Anomalies of the oculomotricity were less sensitive to the treatment.

**Conclusion:** According to our experience, Chitotriosidase is a sensitive and specific marker in diagnosing and monitoring Gaucher's disease. The enzyme replacement therapy through Cerezyme® is an effective and safe treatment of Gaucher's disease. Blood signs (anemia, platelet count); visceral signs (splenomegaly, hepatomegaly) as well as bone involvement showed decisive improvement under the therapy.

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**Key Words:** Cerebroside; Glucocerebrosidase; Enzyme Replacement Therapy; Gaucher Disease; Ceredase; Cerezyme

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## Introduction

Gaucher's disease is a lysosomal storage disorder characterized by the accumulation of glycosyl ceramide in cells of the macrophage/monocyte system. It results from a hereditary deficiency of the lysosomal acid  $\beta$ -glucosidase enzyme. Gaucher's disease is due to mutations involving the  $\beta$ -glucosidase gene, localized in the large arm of chromosome 1 (1q21). Actually about 300 different mutations of this gene are known<sup>[1-6]</sup>. The glucocerebrosides, found inside the red blood cell and white blood cells membranes, are accumulated in large quantities in fibril-like elements in the bone marrow, liver, and spleen (Gaucher's cells).

Gaucher's cells inside the bone marrow will cause bone impairment, osteoporosis or fractures. In the liver and the spleen they will cause organ enlargement; in the blood system anemia, leucopenia and low platelet count are the most common profiles<sup>[1,3,5,7-9]</sup>.

There are three clinical subtypes of Gaucher's disease. Type 1 or the non-neuronopathic form, is the most common form of the disease, comprising 80% of all three types. According to the symptomatology and the clinical burden of the disease, the patient may reach the adult age. Only 30% of individuals with this type of the disease will represent clinical symptoms<sup>[2-4,6,9,10]</sup>.

Type 2 or the acute neuronopathic disease, is the most severe form and the first symptoms are present in the first six months of life, resulting in death during the second year of life. None of our patients was suffering this type of Gaucher's disease. Type 3 or the chronic neuronopathic form, represents the same clinical symptomatology as the type 2, but it has a much slower progression. It is met in 5% of all cases with Gaucher's disease, and its prevalence rates 1:100.000 individuals. This type is seen mainly in a local area of Sweden, the Norrbotten and Västerbotten region, forming thereby a particular picture of the disease<sup>[11,12]</sup>.

All Albanian patients enrolled at the Gaucher's registry were recruited for the study<sup>[13]</sup>. The majority of our patients (9/11) were suffering from type 1 of the disease, and two patients from type 3.

The most common mutations in the overall population are N370S, L444P, 84GG and IVS2+1.

These mutations are seen in 50-60% of the overall casuistic, and 90% of the Ashkenazi Jewish patients. As there is no connection between the mutation type and the clinical severity, it is very difficult to produce a linear phenotype-genotype correlation. Although no straight relation has been found between mutation type and severity, several studies suggest that *some genotypes might indicate a better outcome*<sup>[14,15]</sup>.

DNA analysis is the safest diagnostic method, because the other methods cannot discriminate the heterozygotic form from normal individuals<sup>[4,7,10,12,16-19]</sup>. DNA analysis will find out about 85% of carriers in the overall population and 90% of Ashkenazi Jewish originated carriers. It is also the safest one in the prenatal diagnosis, either by searching the mutation when there is a known risk; or by the genetic connections analysis, when the mutation is not known<sup>[4,6,12,19,20]</sup>.

The enzymatic replacement with Cerezyme® or Imiglucerase, (a recombinant glucocerebrosidase administered intravenously), seems efficacious. The efficacy is proven in the type 1 of the disease. The sooner the treatment it is started, the better results are achieved. The use of Cerezyme® in type 3 has not given satisfying results, especially in terms of improving the neurological signs. Its use is not recommended in type 2 of the disease<sup>[5,19-21]</sup>.

Cerezyme® is a very expensive medicine; its annual cost varies from 100.000 to 550.000 USD, depending on the disease progression. Other alternative therapies are far from approaching the efficacy of Cerezyme®<sup>[8,10,16,21,22]</sup>.

## Subjects and Methods

During the period 2004-2009 in our Service of Pediatrics, UHC 'Mother Theresa' of Tirana, eleven children were hospitalized and treated for Gaucher's disease. 9 children were suffering from type 1, and 2 children from type 3 of the disease. Chitotriosidase values, other biochemical markers and the genetic molecular analysis were performed in our study group. The group was treated with Cerezyme® and a thorough follow-up covering a two-year period of treatment was performed (Tables 1-3).

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An informed consent was received in all cases (from respective parents when the patient was minor); the Service of Pediatrics and the University Hospital Center approved the methodology and the study. Furthermore, the Local Drug Control Office licensed the drug usage for this specific indication.

The casuistic of our clinic consists of 11 patients treated with Cerezyme®. The patients were diagnosed as Gaucher's disease; the onset of the disease anticipated the beginning of the enzymatic replacement treatment with an age span from 5 to 12 years. The group treated with Cerezyme® was composed of 7 males and 4 females.

The criteria of *diagnostic suspicion* were: anamnesis, clinical signs such as tiredness, paleness, abdominal pain, hemorrhagic syndrome (ecchymosis, epistaxis or focal hemorrhages), liver and spleen enlargement, physical and/or mental retardation, low red blood cells count and hemoglobin value, low platelet and leukocyte count, radiological signs showing involvement of long bones (femur, humerus, vertebral column), myelogram, the liver biopsy, the values of the enzyme glucocerebrosidase and of the biomarker chitotriosidase. The diagnostic criteria were adopted from the Belgian Working Group on Gaucher Disease<sup>[23]</sup>. The diagnostic confirmation and the gene mutation localization were performed through the DNA molecular examination in 9 of our patients. The peripheral blood examinations, the myelogram and the skeletal radiology were done in the clinical-biochemical and imaging laboratories of UHC "Mother Theresa", Tirana. No genetic data was available in two patients of our series.

The enzymatic examinations of the biomarker chitotriosidase were performed in Sahlgren's University Hospital, Mölndal Sweden; and the DNA analyses were performed in Children's Hospital & Regional Medical Center, Seattle, USA.

The treatment consisting in the enzyme replacement (Cerezyme®) was supported by Genzyme Corporation, USA. The treatment with Cerezyme® was applied parenterally and the drug was administered with a three hour-infusion through a venous line. The patients suffering from Gaucher's disease type 1 received Cerezyme® with a dosage of 60 UI/kg of body weight every other week; the patients suffering from Gaucher's

disease type 3 received Cerezyme® with a dosage of 120 UI/kg of body weight every other week. The patients are actually under continuous treatment, since the preparation has to be administered *ad vitam*, apart from very rare cases of idiosyncrasy, an occurrence that was never encountered within our group of patients.

Due to the consistent cost of the treatment, the respective dosage of Cerezyme® may be decreased after the pediatric age; at any case the treatment cannot be stopped merely on the ground of slight and transitory side effects. We did not registered serious side effects during the treatment that could warrant the treatment withdrawal.

The dosages we applied are as well suggested from other authors, although there is a wide margin, namely of 30 – 60 UI/kg of Cerezyme® monthly per type 1; double dosages are used for type 3 of Gaucher's disease together with maintenance infusions on a biweekly or even weekly basis<sup>[24]</sup>.

Informed consent was received from parents when patients were minor, and from adult patients. Albanian ethical committee approved the study and the hospital treatment was entirely performed in respect of Albanian ethical and deontological code. Medical records and data were treated anonymously. Direction of the University Hospital Center was notified about the treatment and the results produced.

## Findings

Among our patients, 9 were suffering from the type 1 of Gaucher's disease, and 2 others were suffering from the type 3. All patients were born from normal pregnancies and normal birth deliveries. Within the patients' group no one had any kinship relation with the others. After the diagnosis criteria were met, we initiated the specific treatment within a time delay that varied from 4 to 6 months. Such a time delay was mainly related to the Cerezyme® availability.

The most important clinical signs seen in our patients are shown in Table 1. In Table 2 we describe the hematological values, the data of the

**Table 1:** Signs and symptoms before starting the treatment with Cerezyme®

| Patient | Sex | Actual age | Tiredness | Abdominal pain | Bone pain | Epistaxis<br>Ecchymosis | Spleno-<br>megaly | Liver | Growth<br>retardation | Bone signs<br>(radiological) |
|---------|-----|------------|-----------|----------------|-----------|-------------------------|-------------------|-------|-----------------------|------------------------------|
| 1       | M   | 22         | -         | +              | -         | -                       | ++++              | ++    | -                     | +                            |
| 2       | F   | 11         | +         | +              | -         | -                       | ++++              | +++   | +                     | +                            |
| 3       | M   | 17         | +         | +              | +         | -                       | +++               | +++   | +                     | +                            |
| 4       | F   | 16         | +         | +              | +         | +                       | ++++              | +++   | -                     | +                            |
| 5       | M   | 15         | -         | +              | +         | +                       | +++               | +++   | -                     | +                            |
| 6       | F   | 10         | -         | +              | +         | -                       | ++++              | ++    | -                     | +                            |
| 7       | M   | 9          | -         | +              | -         | +                       | ++++              | ++    | -                     | +                            |
| 8       | F   | 14         | +         | -              | +         | -                       | +++               | ++    | -                     | +                            |
| 9       | M   | 9          | +         | -              | -         | -                       | +++               | +++   | -                     | +                            |
| 10      | M   | 13         | +         | +              | -         | -                       | ++++              | +++   | +                     | +                            |
| 11      | M   | 10         | +         | +              | -         | -                       | +++               | ++    | +                     | +                            |

Note: (-) sign or symptom is lacking, (+) minor sign or symptom, (++) moderate sign or symptom, (+++) prominent evidence, (+++++) massive evidence and/or requiring urgent treatment

myelogram, the enzymatic values of glucocerebrosidase and chitotriosidase performed in all our patients before the treatment was started, as well as the genetic mutations detected in 9 of them.

The parameters of the clinical improvement (liver and spleen reduction in size, bone signs improvement, epistaxis disappearance) and the biological improvement (hemoglobin value, platelet count and the levels of the biomarker chitotriosidase) after the treatment with the specific enzyme (Cerezyme®) was started, are shown in Table 3.

In our case series, two years after the beginning of the treatment, the hemoglobin level was normalized, after it started to increase within the

6<sup>th</sup> month of the therapy. The platelet count was normalized in seven patients after one year of treatment, and in nine patients after two years of treatment. The hemorrhagic syndrome stopped after six months of treatment.

Chitotriosidase values decreased 10-20 times the initial value after one year of treatment, and in one case such a value reached the normal range. The decrease of chitotriosidase levels correlated with the improvement of the clinical signs, which justifies analyzing of this biomarker for a better evaluation of the disease progression, as well as in orientating the necessity for a specific Cerezyme® dosage, an extremely expensive drug. The treatment with Cerezyme® has also improved the visceral and biological signs. Oculomotor

**Table 2:** Genetic, molecular and other baseline data

| Patient | Genotype          | Glucocerebrosidase<br>μkat/Kg<br>(normal value ≥3.2) | Chitotriosidase<br>μkat/L (normal<br>value <40) | Myelogram | Hgb<br>(gr/dl) | Plt<br>(10 <sup>3</sup> /mm <sup>3</sup> ) |
|---------|-------------------|--|---|-----------|----------------|--|
| 1       | No data           | 0.9  | 23.230  | -         | 11.5           | 80   |
| 2       | No data           | 0.68   | 11.800  | +         | 8.8            | 80   |
| 3       | D409H/F213I       | 0.62   | 31.220  | +         | 9.9            | 120  |
| 4       | N370S/D409H+H225Q | 0.99   | 13.687  | +         | 10.2           | 110  |
| 5       | N370S/D409H       | 1.09   | 3191  | +         | 11.1           | 120  |
| 6       | N370S/R47X        | 0.46   | 4348  | +         | 10.1           | 100  |
| 7       | N370S/S107L       | 0.91   | 13.421  | +         | 9.0            | 90   |
| 8       | N370S/R463H       | 0.30   | 2724  | +         | 12.1           | 56   |
| 9       | N370S/L444P       | 0.39   | 1152  | +         | 10.2           | 247  |
| 10      | N370S/D409H+H225Q | 0.22   | 10.342  | +         | 11.5           | 80   |
| 11      | N370S/L444P       | 1.14   | 2330  | +         | 6.4            | 177  |

Note: Myelogram (-) diagnostic negativity; Myelogram (+) diagnostic positivity; Hgb: Hemoglobin; Plt: Platelet

**Table 3:** Overall hematological, visceral, skeletal and chitotriosidase parameters improvement; two years after the treatment with Cerezyme® was started.

| Patient | Type | Hgb (gr/dl) | Plt ( $10^3/\text{mm}^3$ ) | Epistaxis Ecchymosis | Chitotriosidase $\mu\text{kat/L}$ | Spleen volume reduction | Liver | Bone signs | Cerezyme® doses UI/Kg/2 wk |
|---------|------|-------------|----------------------------|----------------------|-----------------------------------|-------------------------|-------|------------|----------------------------|
| 1       | 1    | 17.4        | 101                        | Disappeared          | 1319                              | ++                      | ++    | +          | 60                         |
| 2       | 3    | 10.5        | 223                        | Disappeared          | 264                               | +                       | +     | +          | 120                        |
| 3       | 3    | 14.4        | 182                        | Disappeared          | 134                               | +                       | +     | ++         | 120                        |
| 4       | 1    | 13.6        | 203                        | Disappeared          | 546                               | -                       | +     | +          | 60                         |
| 5       | 1    | 13.3        | 209                        | Disappeared          | No data                           | +                       | +     | +          | 60                         |
| 6       | 1    | 13.1        | 320                        | Disappeared          | 903                               | -                       | +     | ++         | 60                         |
| 7       | 1    | 12.0        | 170                        | Disappeared          | 1374                              | +                       | ++    | +          | 60                         |
| 8       | 1    | 13.6        | 222                        | Disappeared          | 296                               | +                       | +     | +          | 60                         |
| 9       | 1    | 12.0        | 256                        | Disappeared          | 146                               | +                       | ++    | +          | 60                         |
| 10      | 1    | 13.8        | 169                        | Disappeared          | 818                               | +                       | ++    | +          | 60                         |
| 11      | 1    | 13.4        | 280                        | Disappeared          | No data                           | -                       | +     | +          | 60                         |

Note: (-) no improvement; (+) slight improvement; (++) notable improvement; Hgb: Hemoglobin; Plt: Platelet

anomalies were less sensitive to the treatment, probably because the Cerezyme® given intravenously does not pass through the hematoencephalic barrier<sup>[5,8,16]</sup>.

## Discussion

There is a large variety of clinical signs in Gaucher's disease. Spleen enlargement was seen in all our patients, but in six of them it was massive and was accompanied with a sharp pain in the left flank seen also after a light physical exercise, as a result of the splenic capsule tenderness. In three cases, the echography showed spleen nodules and hyperechogenic zones inside the parenchyma. Liver enlargement was found in all our patients, but it was less significant from the spleen enlargement, and it was not accompanied with an increase in the bilirubin and/or liver enzyme values, or with a decrease in the prothrombine level as well as with no changes in the protein electrophoresis profile.

Liver involvement might progress toward the cirrhosis, accompanied with portal hypertension, ascites and esophageal varicosities, but these manifestations were otherwise mainly absent in our group<sup>[5,7,10,20]</sup>.

Bone involvement is very common in Gaucher's disease. The radiological examinations showed

osteopenia of the femoral bone in all our patients, of the humerus in seven of the patients and of at least one vertebral body in three patients. Osteosclerotic changes were seen in four from our eleven patients, and osteolysis only in one patient. Bone pain was present in six children, and in two of them the pain was paroxysmal<sup>[3,5,16,21,22]</sup>.

The bone marrow examination for the detection of Gaucher's cells is important, but it is not pathognomonic. Sometimes a single bone marrow examination may not be sufficient, as the disease has a focal nature. In two of our cases we performed the bone marrow examination twice. The positivity of myelogram data in our patients was high (10/11). The hematological disorders are one of the more constant manifestations of this disease. In our group, the hemoglobin level was decreased in six cases, the platelet count was decreased in nine cases and the white blood cell count was decreased in two cases. Platelet count never reached levels under  $50 \times 10^3/\text{mm}^3$  in any of our patients, and no secondary infection due to leucopenia was met<sup>[8,10,20,21]</sup>.

According to majority of the authors, the glucocerebrosidase enzyme activity in Gaucher's disease is below 30% of normal values. It was below 20% of the normal value in six of our patients, which were two cases of type 3 and four other patients of type 1 of the disease. Other biomarkers, which are related to biochemical changes and multisystemic involvement of the disease, can be evaluated as well. These

biomarkers are chitotriosidase,  $\beta$ -hexosaminidase, angiotensin converting enzyme (ACE) and acid phosphatase.

Among these, the most important is chitotriosidase, levels of which were increased in all our patients, varying from 1152 to 31220  $\mu\text{kat/L}$  (normal range  $\leq 40 \mu\text{kat/L}$ ). However, there is no correlation between these values and the clinical significance of the disease<sup>[10,18,21,25]</sup>.

The genetic molecular examinations were performed in eight patients of type 1 and in one patient of type 3 (Table 2). All patients were affected of a double heterozygotic form, which means they were carrying simultaneously two different mutations. The dominant mutation in the type 1 of Gaucher's disease in our group was **N370S** (8/9), which fully corresponds to the literature data. The second most common mutation in this type of the disease was **D409H**, which was present in four cases, while **L444P** was present in two cases, and **R47X**, **R463H**, **S107L** (rare mutations) were seen each in one patient. The very serious mutation **L444P**, characteristic for the types 1 and 3 of the Gaucher's disease, was not seen in any case in homozygotic form, which does not correlate with other literature data<sup>[2,4,7,8,19]</sup>.

The treatment with Cerezyme®, in the form of a recombinant enzyme provided good results in both types 1 and 3. Liver and spleen reduction in size was achieved in our patients, in 40-50% and 50-60% respectively, two years after the therapy was started, and this corresponds to other casuistics<sup>[5,8,10]</sup>. In two cases a spleen size normalization was also seen. Bone alterations, such as osteopenia, were persisting even after two years of treatment. Osteosclerotic changes, osteolysis and Erlenmeyer sign nevertheless disappeared after two years of treatment.

Cerezyme® side effects such as hypersensitivity reactions, anaphylactic shock, pruritus, reddening, urticaria, angioedema, chest pain, dyspnea, hypotension, coughing and cyanotic reactions are rarely described in the literature and were not met in any of our patients<sup>[10,11,16,22]</sup>.

The results of the actual study are in accordance with the overall opinion of efficacy for Cerezyme®, although our study was an open-label, non randomized and non-blinded one. Another limitation probably is related to the fact

that no control group receiving alternative treatment (such as substrate reduction therapy [SRT] or miglustat) was instituted; other authors have suggested and applied such treatment in combination<sup>[14]</sup>. Anyway, alternative treatments and the option of no treatment, although still in use in isolated cases, widely lack the level of efficacy offered from Cerezyme®.

## Conclusion

Gaucher's disease may be under-diagnosed in Albania, due to the paucity of the sources for performing the genetic evaluation and analysis.

The most common mutation in our patients' group, formed from eleven patients, was **N370S**.

Chitotriosidase was a sensitive and specific marker in diagnosing and monitoring Gaucher's disease. Signs and symptoms in the group were registered at the baseline, and every six months after treatment institution, for a period of two years.

The replacement enzyme, Cerezyme® resulted effective and safe in treating the Gaucher's disease. The patients suffering from Gaucher's disease type 1 received Cerezyme® with a dosage of 60 UI/kg of body weight every other week; the patients suffering from Gaucher's disease type 3 received Cerezyme® with a dosage of 120 UI/kg of body weight every other week. The genetic profile was not decisive in the efficacy prediction; therefore such treatment has to be applied to all patients suffering from Gaucher's disease type 1 and 3, whichever mutations are detected.

The National State Health system must provide some models to reimburse Cerezyme® in Albania, due to proven efficacy of the treatment, as well as due to the extreme costs of the drug, and the necessity for a lifelong uninterrupted treatment.

## Acknowledgment

Albanian ethical committee approved the study and the hospital treatment was entirely performed in respect of Albanian ethical and deontological code.



**Conflict of Interest:** No funding was received for the present work. The actual treatment with Cerezyme® (enzyme replacement) was generously supported from Genzyme Corporation, USA.

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