Gaucher disease type 1: the first experience of enzyme replacement therapy in pediatric practice in Moldova - case report

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Abstract

We report on a case of a little girl patient diagnosed with Gaucher disease (GD) type 1 in her early childhood and our first experience with enzyme replacement therapy (ERT). She was first diagnosed accidentally with enlarged spleen during a pediatric examination when she was three years old, but the family ignored investigations; she was hospitalized for diagnosis at six years old. The GD was confirmed based on: clinical manifestations of left abdominal flank pain, multiple bruising, general weakness, bone pain, low appetite, failure to thrive <5th percentile, minor hepato- and severe splenomegaly, enlarged submaxillary lymph nodes, associated by anemia with normal platelets; low activity of beta-Glucosidase, two found mutations in *GBA* gene, Gaucher cells in bone marrow. The ERT was initiated with Imiglucerase (54 UI/kg/2 wks) two years later after diagnosis, avoiding the splenectomy. Subsequently, the platelets showed the first a promising result, gradually increasing their number every 2 weeks and maintaining it in good parameters till the reported moment (2.5 yrs from the start). The hemoglobin level was appreciated within normal ranges 3 months after ERT start and stabilized completely after 6 months. On the other hand, the red blood count normalized within 20 months of applied therapy. The Lyso-GL-1 decreased by 30% after three months of therapy, no antibodies to Imiglucerase were found. The initial spleen volume (1178.19 cm^3) decreased by almost 60% in 6 months of ERT, reaching absolutely normal dimensions after 9 months. The ERT with Imiglucerase was tolerated very well by the patient, showing a clear improvement of clinical symptoms after 4-6 months of therapy, hematological picture and splenomegaly solving. Even if the little patient had to come every 2 weeks for infusion, her quality of life improved a lot, being a totally happy child, going to school and having friends. The ERT should be initiated immediately after diagnosis to prevent the multisystem complications.

Keywords: Gaucher disease, splenomegaly, Imiglucerase, ERT

Gaucher disease (GD, OMIM #230800, ORPHA355) is a lysosomal storage disorder (sphingolipidosis) caused by mutations in GBA gene, determining the deficiency of the enzyme β-glucocerebrosidase (GBA) activity, involved in the breakdown of complex glycosphingolipids leading to the accumulation of glucosylceramides in the lysosomes of different cells [1,2]. Very rarely, this sphingolipidosis can also be caused by a deficiency in the Glycosylceramidase activator, saposin C [3]. The incidence of this rare progressive hereditary disease is 1 per 40000 - 60000 population, with the exception of the Ashkenazi Jewish ethnicity in which the incidence is estimated to be 1 per 400-850 births [2,4-6]. Almost 300 unique mutations have been described in the GBA gene [7].

GD is characterized by hepatosplenomegaly, cytopenia, bone impairment and, in certain forms,

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neurological affection. Three types of GD are distinguished: type1 named non-neuronopathic; type 2 and type 3 – neuronopathic GD. Type-1 GD is the most common form of disease with the prevalence 90%-95% in Europe and North America with variable clinical manifestations of multisystem affection. The median age of diagnosis is from 10 to 20 years [7-9]. The type 2 of GD occurs in less than 2% of cases and type 3 - in 5% of cases [10,11]. Established on clinical manifestations the diagnosis of GD lasts for several years after the onset of the first symptoms; this is a typical challenge for diagnosis of rare diseases. Nowadays, by using enzyme activity and mutations analysis, it becomes possible to diagnose the disease at a very early stage. The residual enzyme activity is usually approximately 10-15% of normal value [12].

Usually, the clinical manifestations in GD type 1 include the symptoms of multisystem affection: splenomegaly (90%), hepatomegaly (60-80%), fatigue (50%), growth retardation <5th (34%), thrombocytopenia (60–90%), anemia (20–50%), bone crises (30%), avascular necrosis (15%), Gaucheroma (40%), gallstones (32%), lung involvement. Untreated, the disease progresses chronically and the natural course is characterized by the various complications of GD. Generally, if the clinical symptoms appear earlier, for example in the childhood, a more severe glucocerebroside accumulation and course of the disease is suggestive. [2]. The developed ERT is coming to provide the resolution of hepatosplenomegaly, avoidance of splenectomy, normalization of hematological values and physical development, improvement of quality of life, increasing in life-expectancy and prevention of multisystem complications.

Case description

We report a case of a little girl patient diagnosed by Gaucher disease in her early childhood and our first experience of ERT applied in this case. This girl is the first child in a non-consanguinous Moldovan couple of two healthy parents, from the 3rd pregnancy of mother, obtained by IVF, because of her two ectopic pregnancies and ensuing tubar infertility. She was born at term, with normal weight at birth (wt_0=3260 g), with Apgar score of 7/7 and normal neuropsychomotor development after birth. At one month old, the girl has been presented by prolonged neonatal jaundice and Iron deficiency of 1st degree, at three months old there was detected a mild hip dysplasia. During the first 2 years of life, she was admitted several times to the hospital with functional gastric problems as colitis, transversoptosis, dolichosigma, constipations. At three years old the enlarged spleen (103 mm) was identified during a pediatric control, for which hematological consultation was recommended, ignored by the patient's family.

At six years old the child was hospitalized in the Hematology Department, complaining of pain in the left abdominal flank, multiple bruising, general weakness, bone pain, low appetite, failure to thrive under 5th percentile, enlarged abdomen due to hepatosplenomegaly, and enlarged submaxillary painless lymph nodes (0.8-1.0 cm). The investigations put in evidence anemia (Hemoglobin (HGB) - 10.4 g/dL, Red Blood Cells (RBC) - 3.3x 10^{12}/L) with normal platelets. The blood biochemistry was normal, except the high level of direct bilirubin (6 μmol/L, *ref. val. 0-3.42).* Abdomenal ultrasound showed the pronounced enlarged spleen (140 mm) and liver (DL=115 mm, SL=47 mm). Summarizing the clinical parameters, one of the first potential diagnosis was considered Gaucher disease and we decided to use the enzyme method, for the first accessible in Moldova.

As a consequence, the activity of beta-Glucosidase was 60.8 - below its reference range (*200-2000 pmol/ spot*20h*). Other controlled enzymes as acid sphingomyelinase - 506 (*ref.val. 200-3500 pmol/ spot*20h*) and beta-galactosidase - 0.52 (*ref.val. 0.5-3.2 pmol/spot*20h*) were within their reference ranges. So, the investigations followed by the mutations analysis which had shown two heterozygous mutations in *GBA* gene: *c.[1226A>G]/[1265_1319del].* The mutation *c.[1226A>G]* leads to the substitution of *Asn* by *Ser* in the position 409 of protein, but the mutation *[1265_1319del]* is characterised by a deletion of 55 pb in exon 9 of the gene. While these specific analyses results were obtained, a traditional sternal puncture was performed, which identified Gaucher cells within moderately cellular polymorphic bone marrow with normal megacaryocytes and platelets. Two mutations found in *GBA* gene, additionally to the clinical manifestations of anemia, hepatosplenomegaly, bone pains, failure to thrive, low enzyme activity and Gaucher cells in bone marrow confirmed the Gaucher disease.

For the period after diagnosis, the possibility of ERT initiation was uncertain and the little patient was monitored every 3 months, being invited to visit the doctor. The aim was to avoid splenectomy and to obtain the solutions for ERT which was not applied before in Moldova. It was followed by manifestations of severe anemia (HGB-10.9-9.1 g/dL, RBC-3.96-2.9 x 10^{12}/L) and low platelets (124-88x10^9/L, *ref. val 150-500*), dependent of blood transfusions. Additionally, the blood investigations evidenced a normal biochemistry except the persistent hyperbilirubinemia, including the both its fractions. At seven years old, one year after diagnosis, the little patient was hospitalized because of an acute nonspecific inguinal lymphadenopathy, solved well with antibacterial therapy.

Preparing for ERT, many investigations were done to complete the child's GD picture. One and half years later after diagnosis, the Lyso-GL-1 was tested as a key biomarker of GD. The high value of 696.8 ng/mL *(ref.val. 0.0-14.0)* of Lyso-GL-1 as a direct result of acid β-glucosidase deficiency and disease severity confirmed the urgent necessity of ERT. Beside the persistent anemia, the biochemistry always indicated good parameters (transaminases, urea, creatinine,

cholesterol, tryglycerides, alkaline phosphatase, glucose, vit. B_{12}, AFP, cholinesterase, P, Ca, Fe, Feritine, 25(OH)-Vit.D), excepted hyperbilirubinemia and additionally low dHDL-Cholesterol. Immune test revealed normal IgA, IgE, IgM, IgG. Ultrasound monitoring (x 3 times) showed augmented size of liver (DL=117-111-121 mm) and spleen (150-145-157 mm). Abdominal MRI established the exact dimensions of internal organs. The liver was found heterogenous and enlarged of minimum degree (DL=136 mm, SL=36 mm), without abnormalities like focal lesions and hyperplasia, normal bile ducts, piriform gallbladder, size 7.2 x 2.7 cm, no gallstones. But the spleen was found extremely enlarged (17.1 x 6.5 x 10.6 cm–vertical x transversal x AP). No other irregularities were found. Also, data for aseptic necrosis of the femoral head were not determined by the MRI of coxo-femoral joint; a low bone density at left hip and normal at lumbar spine level was appreciated by DEX Scan.

The ERT was initiated with the Imiglicerase two years from the diagnosis and the case was successfully managed to avoid the splenectomy. Before this, the little patient was in relatively satisfactory condition, went to the school, but she accused chronic fatigability, abdominal pains and episodes of morning sickness against the background of chronic anemia. We obtained the informal consent from the family of our patient for hospitalization every two weeks in Institute of Mother and Child for infusions with Imiglucerase and continuous monitoring of weight, blood count, biochemistry, abdominal ultrasound and additional specific tests (Lyso-GL-1, Antibodies). The first doses of 54 UI/kg/2wks of Imiglucerase (suggested 40-60 UI/kg/2wks) were applied in Intensive Care Unit with premedication and caution as recommended, and were well tolerated.

Subsequently of Imiglucerase administration and blood analysis every 2 weeks we observed that the platelets were the first which showed a promising result, gradually increasing their number every 2 weeks and maintaining it in good parameters till present (2.5 yrs from start). The HGB level was appreciated within normal ranges 3 months later after ERT starting and stabilized completely after 6 months of applied therapy.The RBC were normalized 20 months later after ERT outset. Three months after ERT start the Lyso-GL-1 was controlled and decreased by 30% and no antibodies to Imiglucerase were found. At the same time, the patient noticed an improvement in the general condition and her appetite.

Another followed-up marker was the Spleen Volume (SV). The initial SV (1178.19 cm^3) came to be almost in normal size 6 months after Imiglucerase administration, it decreased by about 60%, after which it continued to reduce its size till absolutely normal. The SV came to normal dimensions after 9 months and continues to stay in those ranges. During the ERT with Imiglucerase the SV was observed as the most sensitive criterion to the dose variations. Once the dose of Imigucerase was decreased closer to 40 UI/kg/2wks due to weight adding and thrive of patient, the spleen increased in volume and the dose had to be readjusted closer to 60 UI/kg/2wks. The liver size did not change during Imiglucerase therapy, sometimes we determined decrease of protein level and increase of PTT, spontaneously resolved, which obliged us to pay attention to liver function; a slight hyperbilirubinemia persisted.

In conclusion, the patient showed a clear improvement in clinical symptoms after 4-6 months of therapy, hematological picture and spleen volume normalized as the effect of ERT with Imiglucerase. Even if the little girl had to come every 2 weeks for infusion, her quality of life improved a lot being a totally happy child, going to school and having friends. Summarizing, in this case of GD, the child's disease had a mild evolution and we could avoid the splenectomy till ERT was started. The ERT with Imiglucerase was very well tolerated, showed very good results in clinical manifestations, in hematological parameters and splenomegaly solving and it should be initiated as soon as possible to prevent multisystem complications.

References

1. Elstein D, Abrahamov A, Hadas-Halpern I, Zimran A. Gaucher's disease. Lancet. 2001;358:324-327.
2. Niederau Claus. Gaucher Disease. 3rd edition- Bremen: UNI-MED, 2017. P. 112.
3. Vaccaro AM, Motta M, Tatti M, Scarpa S, Masuelli L, Bhat M, et al. Saposin C mutations in Gaucher disease patients resulting in lysosomal lipid accumulation, saposin C deficiency, but normal prosaposin processing and sorting. Hum Mol Genet. 2010;19:2987–2997.
4. Linari S, Castaman G. Clinical manifestations and management of Gaucher disease. Clin Cases Miner Bone Metab. 2015;12:157-164.
5. Giraldo P, Roca M. Therapeutic targets in Gaucher's disease [Objetivos terapéuticos en la enfermedad de Gaucher]. Med Clin (Barc). 2011;137 Suppl 1:46-49. Spanish
6. Grabowski GA. Phenotype, diagnosis, and treatment of Gaucher's disease. Lancet. 2008;372:1263–1271.
7. Hruska KS, LaMarca ME, Scott CR, Sidransky E. Gaucher disease: mutation and polymorphism spectrum in the glucocerebrosidase gene (GBA). Hum Mutat. 2008;29:567–583.
8. Stirnemann J, Vigan M, Hamroun D, Heraoui D, Rossi-Semerano L, Berger MG, et al. The French Gaucher's disease registry: clinical characteristics, complications and treatment of 562 patients. Orphanet J Rare Dis. 2012;7:77.
9. Stirnemann J, Belmatoug N, Camou F, Serratrice C, Froissart R, Caillaud C, et al. A Review of Gaucher Disease Pathophysiology, Clinical Presentation and Treatments. Int J Mol Sci. 2017;18:441.

10. Kraoua I, Sedel F, Caillaud C, Froissart R, Stirnemann J, Chaurand G, et al. A French experience of type 3 Gaucher disease: Phenotypic diversity and neurological outcome of 10 patients. Brain Dev. 2011;33:131-139.
11. Mignot C, Doummar D, Maire I, De Villemeur TB; French Type 2 Gaucher Disease Study Group. Type 2 Gaucher disease: 15 new cases and review of the literature. Brain Dev. 2006;28:39-48.
12. Neufeld EF. Lysosomal storage diseases. Annu Rev Biochem. 1991;60:257–280.