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Clinical and Diagnostic Findings of 19 Gaucher Patients in Albania

V Velmishi[1]*, D Bali[2], E Dervishi[1], V. Durro[3] and P Cullufi[1]

[1]Pediatric Gastrohepatology Service, UHC "Mother Teresa", Tirana, Albania
[2]Pediatric Hematology Service, UHC "Mother Teresa", Tirana, Albania
[3]Hospital Planning Directory, Ministry of Health, Tirana, Albania

Abstract

Aim: Gaucher disease is a multisystemic disorder characterized by glucocerebrosidase enzyme deficiency. The aim of this study was to present clinical aspects and diagnostic data of 19 patients (17 type 1, 2 type 3) in our service.

Methods: Clinical findings, genetic analysis, laboratory work up, liver and spleen volumes were analyzed for 19 patients.

Results: Mean age was 17 years (5-32 years); mean age at diagnosis was 11, 4 years (5-31 years). Most common presenting symptom was splenomegaly (all patients). Most frequent mutation was heterozygous N370S. One patient had severe anemia before the treatment. 16 patients had thrombocytopenia. All patients had high level of chitotriosidase before the treatment (240 times higher than normal value).

Conclusion: There is a large variety of clinical signs in Gaucher disease. In our experience a proper investigation of patient followed by further expensive examinations is the cornerstone of diagnostic.

Keywords: Gaucher disease; Glucocerebrosidase; Chitotriosidase

Introduction

Gaucher disease is a lysosomal storage disease characterized by a genetic disruption in the metabolic breakdown of glucocerebroside caused by a lack of the enzyme glucocerebrosidase. This lipid storage disease was first described in a case report by Philippe Charles Ernest Gaucher [1]. Brill first published the term "Gaucher disease" and he was the first to recognize the autosomal recessive heredity [2]. The neuronopathic form in children was subsequently reported. Many decades passed before Brady and his colleagues found evidence that the disease is based on a deficient glucocerebrosidase enzyme activity [3]. Reliable biochemical diagnosis of the disease was made possible. Measurement of reduced activity of glucocerebrosidase in leucocytes is still the diagnostic gold standard. Later, the relevant gene was located on the long arm of chromosome 1 [4]. Glucocerebrosidase was first isolated from the human placenta in 1977 but it took some time before investigators realized that biochemical modification is necessary for the effective uptake of the enzyme in macrophages. The modified enzyme proved to be effective in clinical studies and was licensed as the first medicine for the treatment of a lysosomal storage disease [5]. Soon aglucerase was replaced by genetically engineered imiglucerase. Another approach to therapy is based on inhibition of the synthesis of the stored substance by substrate inhibitors. Cox et al. first showed that the oral substrate inhibitors N-butyledeoxynojirimycin (miglustat) have a clinical effect [6]. Since 2002, miglustat has been licensed for treatment of mild to moderate forms of Gaucher disease (type 1) in adults for whom enzyme replacement therapy is unsuitable. Enzyme replacement therapy has been the standard therapy for non–neuronopathic forms and complications of Gaucher disease. This treatment has no significant side effects and enables patients who have been diagnosed early to live a normal life.

There are three clinical subtypes of Gaucher 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 reaches the adult age. Only 30% of individuals with this type of the disease will represent clinical symptoms [7-12]. The incidence is 1:40000 to 1:60000.

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 (Incidence <100000). 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 case with Gaucher disease, and its incidence rates 1:50000 to 1:100000 individuals. This type is seen mainly in a local area of Sweden, the Norrbotten and Vasterbotten region, forming thereby a particular picture of the disease [13,14].

Methods

As of 2004, we have diagnosed 19 patients with Gaucher disease. 17 patients are suffering from type 1 and two patients are type 3. Mean age was 17 years (5-32 years); mean age at diagnosis was 11.4 years (5-31 years). We have enrolled for each patient personal data, clinical and laboratory findings and the diagnostic tools. The diagnostic criteria were adopted from the Belgian Working Group on Gaucher disease. The enzymatic examinations of the biomarker chitotrioksidase were performed in Sahlgren's University Hospital, Molndal Sweden; and the DNA analyses were performed in Children`s Hospital & Regional Medical Center, Seattle, USA.

Clinical and laboratory findings

Before the treatment we have registered for each patient spleen and liver size, platelet count, hemoglobin level, bone pain and bone crisis. Clinical parameters were analyzed using the following cut points:

- Anemia is defined according to age and gender norms for

***Corresponding author:** V Velmishi, Pediatric Gastrohepatology Service, UHC "Mother Teresa", Tirana, Albania, E-mail: tutimodh@yahoo.com

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hemoglobin concentrations, as follows: <12 g/dl for males >12 years; <11 g/dl for females >12 years; < 10.5 g/dl for children ages 4-12 years.

- Thrombocytopenia is categorized as mild or none (>120 × 10^3 /mm^3), moderate (60-120 × 10^3 /mm^3), or severe (<60 ×10^3/ mm^3).
- Splenomegaly** (spleen volume in multiples of normal) is scored as mild or none (≤ 5), moderate (>5 to ≤ 15), or severe (>15).
- Hepatomegaly** (liver volume in multiples of normal) is scored as mild or none (≤ 1.25), moderate (>1.25 to ≤ 2.5) or severe (>2.5).
- Bone pain is defined as being present if the patient reported this event as occurring in the 30 day interval before the medical visit.
- Bone crisis was defined as present if the patient reported this event at the time of medical visit. The ICGG Gaucher Registry defines bone crises as "Pain with acute onset that requires immobilization of the affected area, narcotics for the relief of pain and may be accompanied by 1 or more of the following: periosteal elevation, elevated white blood cell count, fever, or debilitation > 3 days".

**Hepatomegaly and Splenomegaly are measured by ultrasound, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) is reported as Multiples of Normal (MN) size predicted for body weight: approximately 2.5 % of body weight for liver and 0.2 % for spleen.

Genetic and other baseline data in diagnostic confirmation

We have completed another table with data about genotype, sex of patient, actual age, genotype, glucocerebrosidase activity, level of chitotriosidase and bone marrow biopsy.

Results and Discussion

Among our patients, 17 are diagnosed with type 1 Gaucher disease, and two others with type 3. Within the patients group, we have 3 relationship of the first degree (two couples brother –sister type 1 and one couple brother sister type 3).

The most important clinical sign presented was splenomegaly, 11 patients presented severe splenomegaly and 8 others moderate splenomegaly (Figure 1). As a result of glucocerebrosidase accumulation, many patients with non-neuronopathic form of Gaucher disease suffer splenomegaly early in life, which is usually painless at onset. The spleen can subsequently enlarge up to twenty times its normal size leading to upper abdominal symptoms and a feeling of early satiety. Splenic infarctions causing abdominal pain are common.

An enlarged liver is another typical symptom. The liver is usually more than one and half times to twice the size of the upper norm [15,16]. In our group 14 patients (74%) presented hepatomegaly (5 patients severe form and others mild to moderate form). Liver cirrhosis is rare in Gaucher disease, although 80% of all Gaucher patients have hepatomegaly [15-17].

With pronounced hepatosplenomegaly the hematological test may demonstrate pancytopenia. There is often no leucocytopenia, but anaemia and thrombocytopenia (<80000/µl) are frequent. As the disease progresses, the platelet count can fall to <20000/µl. Bleeding tendency with petechiae and hematomas may be consequence of low platelet counts of coagulation disorders with prolongations of the PPT [18]. In our study we found 13 patients with anaemia. One of them presented hemoglobin level 6.4 g/dl and others had moderate form of anaemia. 16 patients presented thrombocytopenia (84%). One of them presented severe thrombocytopenia, 5 patients a moderate form and 10 others a mild form.

There is a high prevalence of skeletal pathology in patients with Gaucher disease and this is often associated with considerable pain, limitations in mobility and an extremely negative impact on the quality of life [19-21]. The exact mechanism of bone infiltration by Gaucher cells has not yet been clarified. It is assumed that the bone changes occur as a result of bone marrow infiltration by Gaucher cells. We found 7 patients (37%) presenting bone pain according to our criteria and 2 patients (10.5%) presenting bone crisis.

As the diagnosis of Gaucher disease has considerable consequences and requires expensive therapy, finding a reduced glucocerebrosidase activity in leucocytes should be confirmed with identification of gene defect. To date, over 200 different mutations have been found in patients with a chronic non–neuronopathic form. In addition to PCR, the reverse hybridization technique is also used [22]. The genotype phenotype correlation is unfortunately relatively weak [23,24]. The N370S mutation is very rarely seen in patients with neuronopathic symptoms and homozygosity for the N370S mutation is often related with a particular mild form [23,24]. In type 2, there is an abundance of different genetic changes, including point mutations, splice junction mutations, deletions, fusions and recombinations. The L 444P mutation is common in the neuronopathic form, while the N370 S mutation is very rarely found [23]. In the neuronopathic variants, genetic changes probably lead to particulary severe reduction of glucocerebrosidase; other or additional changes in comparison to the non-neuronopathic type are not known [24]. The genetic frequency of the type 3 in parts of Norrbotten is also characterized by the particularly frequent occurrence of the L444P mutation. A detailed mutation analysis together with genealogical research has shown that the frequency of type 3 in Norrbotten can be traced back to a sole mutation in the 15-16th century [25]. In prenatal deaths, molecular genetics null mutations have recently been reported [26]. A large genetic heterogeneity has been reported, even for patients with an acute neuronopathic course [27,28]. In our study the most important genotype is heterozygote mutation N370S (16 patients=84%) (Table 1). We had 7 patients N370S/D409H;

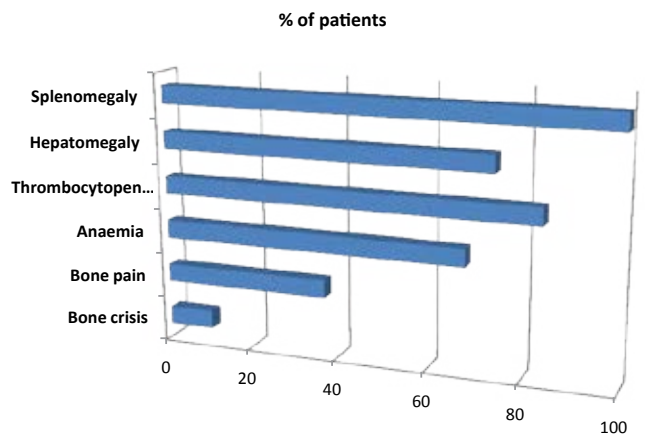

Figure 1: Presentation in graphics of clinical findings in our group of 19 patients.

Patient	Sex	Actual age	Genotype	Glucocerebrosidase µkat/kg(≥ 3.2)	Chitotrioksidase µkat/L(<40)	Bone marrow biopsy
1	M	24	-	0,90	23230	-
2	F	14	-	0,68	11800	+
3	M	22	N370S/F2131	0,62	31220	+
4	F	18	N370S/D409H	0,99	13687	+
5	M	18	N370S/D409H	1,09	3191	+
6	F	13	N370S/R47X	0,46	4348	+
7	M	11	N370S/S107L	0,91	13421	+
8	F	17	N370S/R463H	0,30	2724	+
9	M	12	N370S/L444P	0,39	1152	+
10	M	13	N370S/D409H	0,22	10342	-
11	M	13	N370S/L444P	1,14	2330	+
12	M	12	N370S/S107L	0,87	31221	-
13	M	15	N370S/L444P	1,01	13400	-
14	M	10	N370S/D409H	0,64	5400	+
15	F	32	N370S/D409H	0,90	2700	+
16	F	5	N370S/D409H	0,26	3580	-
17	M	11	N370S/D409H	0,90	3920	-
18	F	30	N370S/L444P	0,71	2110	-
19	M	32	N370S/L444P	1,06	2400	-

Table 1: Genetic and other laboratory data in 19 patients.

5 patients N370S/L444P; 2 patients N370S/S107L; 1 patient D409/F2131; 1 patient N370S/R463H.

The glucocerebrosidase measurement provides a definite diagnosis in homozygous mutation carriers of the glucocerebrosidase gene. In case of typical clinical presentation and markedly reduced glucocerebrosidase activity in leucocytes, the diagnosis of Gaucher disease is confirmed. The measurement of glucocerebrosidase activity should be performed in a laboratory experienced in performing and interpreting this measurement. In our study the level of glucocerebrosidase was found under the normal value in all patients.

The measurement of chitotriosidase is an important laboratory chemical test for Gaucher disease. In patients with Gaucher disease this enzyme is typically massively elevated, often around one hundred to one thousand times the normal value, whereas there is a smaller increase in other lysosomal storage diseases [29-32]. The chitotriosidase value is a helpful tool for deciding on initiation of enzyme therapy and for monitoring treatment outcome. Relapse of the disease due to inadequate therapy can easily be recognized [33]. Chitotriosidase should only be determined at specialized laboratories. We have observed in our group that level of chitotriosidase was increased in all patients. The mean value was 240 times greater than normal value.

Since the introduction of the enzyme activity measurement, the role of bone marrow biopsy has been less significant. Gaucher storage cells are unspecific proof of Gaucher disease as the typical, large ballooned, wrinkled–paper–like storage cells in the cytoplasm may also occur in other diseases (histiocitytosis, thalassemia, granulomatous diseases, etc.) or can resemble foam cells with Niemann Pick disease type A/B or type C. Irrespective of the specific, conclusive laboratory tests, approximately 60% of all Gaucher disease diagnoses are still made via a bone marrow biopsy or histology of a surgically removed spleen. In our group of patients the bone marrow biopsy is performed for each patient and we found 11 patient presenting Gaucher cells.

Conclusion

Gaucher disease has been under diagnosed in Albania because the lack of sources for performing expensive analysis. Nowadays we have created a better experience in diagnosing 19 patients due to collaboration with some specialized centers abroad.

The most common clinical sign in our group of patients was splenomegaly. One of the most laboratory findings in our patients was thrombocytopenia. The most frequent mutation that we found was N370S.

Measurement of glucocerebrosidase activity, genotype analysis and the level of chitotrioksidase were the most expensive examinations. Biopsy bone marrow is a routine examination in our center for diagnostic of gaucher cells

A proper investigation of each patient with hepatosplenomegaly combined with some specific analysis unfortunately expensive is the diagnostic key of Gaucher disease.

Author's Contribution

V Velmishi collected clinical data and drafted the manuscript. D Bali performed the statistical analysis. E Dervishi and V. Durro carry out the corresponding reference. P Cullufi helped to draft the manuscript. All authors have given the final approval of the version to be published.

Consent

Written informed consent was obtained from patients (adults) or patient's parents.

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