Gaucher disease

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Gaucher disease (GD) is the most common lysosomal storage disease. GD is caused by the deficiency of the enzyme glucocerebrosidase (GBA), required for the degradation of glycosphingolipids. Mutations in the GBA1 (acid-β-glucosidase) gene, an 11 exons gene located on chr. 1q21-22 and coding for a 497 amino acid protein, are responsible for the disease. Nearly 300 mutations (frame-shift mut., point mut., deletions, insertions, splice site mut., recombinant alleles) are known and classified based on the phenotypic correlation as:
- “null”, 84dupG (84 GG), no enzyme production, the phenotype is related to the second allele,
- “severe”, 1448T>C (L444P), enzymes are produced but, when inherited with a null or another severe mutation, are usually associated with GD type 2 or 3, and
- “mild”, 1226A>G (N370S), only associated with GD1.

GD is an autosomal recessive disorder with a prevalence, most likely underestimated, in the general population of 1/40000 births (vs Ashkenazi Jewish of 1/850, carrier rate 1/17). GBA deficiency results in the accumulation of its immediate substrates, glucosylceramide and its deacetylated form, glucosylsphingosine, predominately in lysosomes of the reticular endothelial system cells: Gaucher cells are characterized by striated "wrinkled tissue paper" cytoplasm.

GD is a multi-system disorder characterized by (hepato)-splenomegaly, peripheral blood cytopenias (anemia, thrombo-), bone disease, gammopathies w/wo malignancies and, in some patients, neurological manifestations. GD has a continuous spectrum of severity and it is sub-classified into three sub-types based on the neurological features:
- **Type 1** (OMIM # 230800) 95% - chronic non-neurological, characterized by the lack of CNS involvement; 1/40000-60000 non Jewish, 1/600-850 Ashkenasi Jewish.
- **Type 2** (OMIM # 230900) 1% - severe neuronopathic, at infantile onset, with a life expectancy <2 years.
- **Type 3** (OMIM # 231000) 5% - attenuated chronic neurological symptoms, with a pathognomonic supranuclear horizontal gaze palsy, accompanied by visceral involvement and survival into adulthood.

In children, the most common clinical manifestation are splenomegaly (95%), hepatomegaly (87%), anemia (40%), thrombocytopenia (50%) and growth retardation (34%), while bone pain and bone crisis are less common than in adults (27% and 9%, respectively).

If untreated, the disease progresses with age, resulting in hematological and bone disease, irreversible organ damage, morbidity, reduced quality of life, and even a shorter life-expectancy.

Skeletal involvement can manifest as avascular osteonecrosis, joint collapse, osteoporosis, and fractures. It is one of the most disabling complications with a major impact on quality of life.

Moreover, a strict association between GD and B-cell malignancy has been described. GD patients show an increased risk of non-Hodgkin's B-cell lymphoma, polyclonal gammopathy and multiple myeloma. The precise mechanism responsible of this association is still unknown. However, the increased risk of malignancy can contribute to the reduced life expectancy in GD patients. The association with hematological B-cell malignancy has been reported even in the pediatric population.

Treatment modalities include various supportive therapies (pain reduction, blood transfusions, orthopedic surgery) combined with two major therapeutic approaches for GD1:

**Enzyme Replacement Therapy (ERT):**
- Alglucerase *(Ceredase; Genzyme Corp)*
- Imiglucerase (Cerezyme; Genzyme Corp)
- Velaglucerase alfa (VPRIV, Shire Human Genetic Therapies, Inc)
- Taliglucerase alfa (ELELYSO, Pfizer Inc)

and Substrate Reduction Therapy (SRT):
- Miglustat (Zavesca, Actelion Pharma., Switzerland)
- Eliglustat tartrate, (Genz-112638; Genzyme Corp)

The aim of ERT is to provide the appropriate amount of the enzyme to permit excess material degradation. Because ERT does not cross the blood brain barrier, it is not indicated for GD3 and GD2.

The aim of SRT is to minimize the amount of production and the intracellular accumulation of excess glucosylceramide.

ERT with recombinant β-glucocerebrosidase has been demonstrated to be safe and effective in preventing and/or reversing many clinical manifestations of GD, including hepatosplenomegaly, cytopenia, growth and bone disease.

Since the availability of effective therapies, expanded newborn screening programs on dried blood spots (DBS) for the detection of GD and other lysosomal storage diseases, have been advocated for many years. The expanded newborn screening program is currently accessible in Italy, even though it is not available in all areas of the Country.

According to the International Collaborative Gaucher Group Registry data, the diagnosis of GD1 is normally reached only 10-15 yrs after the onset of symptoms. GD pts. are most likely to be referred to hematologists, because the most common disease presentation is splenomegaly with cytopenia. Only a minority of hematologists-oncologists consider GD in the differential diagnosis, even in the presence of all its typical signs and symptoms. Missing a diagnosis of GD in a patient presenting with splenomegaly may lead to a delayed treatment initiation and an increased disease-related morbidity and mortality; while a well-established therapy for this condition is available. Moreover, a missed diagnosis could mean that a patient may have to undergo invasive procedures, such as BM aspiration.

Since two thirds of pts have clinical manifestations of GD already in childhood, it was considered appropriate to develop an algorithm (Figure 1) to support clinicians in promoting a timely diagnosis and early access to therapy for pediatric (<18 yrs) pts with GD1. [Di Rocco M et Al, Ped Blood & Cancer 2014;61:1905-09]

After a congruous waiting period an observational multicentre cross-sectional study (GAU-PED study) has been set up to evaluate the prevalence of GD patients among children referred to the haematology paediatric units for splenomegaly and selected on the basis of the indications contained in the diagnostic algorithm.

Patients are screened for the GBA activity, by means of a DBS sample. GBA deficiency is confirmed using the gold standard GBA analysis.

The GAU-PED study is still ongoing. During the first 18 months of accrual, a total of 47 DBS have been collected from 18 centers, after parental consent. DBS values under 5 pmol/punch(1)/h(1)were found in 19/47 patients (40%). These patients have been recalled for the conventional enzymatic test. The diagnosis of GD has been confirmed in 5/19 (26%) DBS positive patients. In all 5 patients the genetic analysis has been consistent with GD.

Overall, in the tested population, the prevalence of GD is 10.6% (95% CI, 4 - 24%) equal to 5/47 enrolled patients.

Our preliminary results support the use of DBS as screening test for GD in a selected population of children with splenomegaly and/or thrombocytopenia considered at increased risk for the disease. The use of an appropriate diagnostic algorithm is useful to increase awareness of GD among pediatric hematologists and to shorten the time to diagnosis. Taking in consideration the long life expectancy of pediatric GD patients, the early diagnosis will have a strong impact on health and quality of life.