Review Article

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Gaucher disease: Recent advances in the diagnosis and management.

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Abstract

Gaucher disease is a rare genetic disorder characterized by the deposition of glucocerebroside in cells of the macrophage-monocyte system. Gaucher disease is an inborn error of metabolism that affects the recycling of cellular glycolipids. This disease is a consequence of deficiency of the enzyme glucocerebrosidase. It causes bone pain, anemia, enlarged organs, painful belly and bruising and bleeding problems. There are many types of Gaucher disease, all cause similar symptoms in the organs and bones. Some forms of the disease also affect the brain. There is no cure for Gaucher disease, but a variety of treatments can help control symptoms, prevent irreversible damage and improve quality of life. Enzyme replacement therapy is the primary form of treatment for Gaucher disease.

Introduction

Gaucher disease (GD), is one of the commonest lysosomal storage disorders, is caused by mutation of β-glucocerebrosidase enzyme (GCase), leading to the storage of glucocerebroside (monosaccharide) and other glycolipids in various tissues including, liver, spleen, bone marrow, kidneys, lungs and bone marrow resulting in systematic manifestations [1]. Its incidence is approximately 1/40,000 to 1/60,000 births in the general population, but it is rising to 1/800 in Ashkenazi Jews (Eastern European) Jewish population with a carrier frequency of 6% compared to 0.7% to 0.8% of the non-Jewish population[2].

History:

Gaucher disease was first described by Philippe Gaucher in 1882 in a patient with splenomegaly [3]. He described abnormal histiocytes in the tissues of a 32-year-old woman who died of cachexia and massive hepatosplenomegaly as he did autopsy, he discovered that the spleen itself had enlarged cells (Now known as Gaucher cells) He emphasized that the enlarged spleen is a hallmark of the disease in addition to hepatomegaly [4].The eponym “Gaucher Disease” was first introduced by Mandlebaum who recognized the disease as a multi-systemic chronic disease involving the liver, spleen, bone marrow and lymph nodes [5]. In 1927, Oberling et al,discovered the neurologic component of Gaucher's disease which eventually became known as type 2. Babies with type 2 usually die around the age of two years due to its rapidly progressive neurodegenerative nature [6]. Starting in the 1950s, through early 1960s, researchers noticed adulthood onset of various neurological symptoms, cognitive disorder and blood problems; this was described as type 3 [7]. In 1965 Roscoe Brady elaborated the inherited deficiency of lysosomal glucocerebrosidase as the key metabolic defect in Gaucher disease [8]. Years later, enzyme replacement therapy was applied by the same group [9].

Pathophysiology

The signs and symptoms of Gaucher disease can be categorized into; visceral, hematologic and skeletal manifestations; the visceral organis including enlargement of the liver and the spleen. Hematological manifestations are due to cerebroside accumulation in bone marrow producing reduction in blood cells synthesis causing bleeding tendency, anemia, so that increase incidence of infection due to leukopenia. Also, cerebroside accumulation in the spleen is causing excessive break down of red blood cells. Skeletal components can include generalized bony aches, osteonecrosis with subsequent pathological bone fracture and bone deformity. Much of these skeletal abnormalities are attributed to the accumulation of glucocerebroside-laden macrophages in the bone-marrow where they limit blood flow and the delivery nutrients and oxygen which can result in intense pain, bone cell necrosis, low bone density, and growth abnormalities. The pathologic hallmark of Gaucher disease is Gaucher cells in the macrophage-monocyte system. These cells have a characteristic wrinkled-paper appearance, resulting from intracytoplasmic substrate deposition. [10]

Types of Gaucher disease

GD has 3 main types, namely, non-neuronopathic (type I), acute neuronopathic (type II), and chronic neuronopathic (type III), primarily based on the central nervous system involvement. There are 2 rarer subtypes, the perinatal-lethal form and the cardiovascular form. The perinatal lethal type can begin before birth or in early infancy. Type I affects spleen, liver, bone, and bone

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marrow while, Type II GD manifests in early childhood with severe neurological manifestations and death usually occurs before the age of 2 years. Type III may also have significant visceral and lung involvement apart from neurological manifestations, which are less severe as compared to type II [11].

Clinical presentation:

Gaucher disease type 1 (GD1), manifested by splenomegaly, blood disorders, orthopedic complications and lack of neurological symptoms however, Gaucher disease type 2 (GD2), manifested by hepatosplenomegaly and central nervous system involvement within the first year of life. Furthermore, Gaucher disease type 3 (GD3), manifested by nervous system involvement in childhood. These forms of the disease share the same defect in the enzyme glucocerebrosidase; however, the distinct subtypes help in establishing the correct diagnosis and subsequent treatment plan [12,13].

Gaucher disease can present with additional several signs and symptoms, depending on the underlying type as follows:

- Impaired smell and cognition (Type I)
- Serious convulsions, hypertonia, intellectual disability and apnea (Type II)
- Myoclonus, seizures, dementia and ocular muscle apraxia (Type III)
- Parkinsonism.
- Severe joint pains, especially hips and knees.
- Osteoporosis
- Yellowish-brown skin pigmentation.

Diagnosis

GD is clinically assumed when there are at least two of the following findings: hepatosplenomegaly, thrombocytopenia +/− anemia, characteristic bone lesions, or signs of CNS involvement in GD2 or GD3 [14]. However, clinical findings alone are not diagnostic; GD biomarkers confirmation is mandatory. The current gold standard for diagnosing GD is the detection of reduced β-glucocerebrosidase (GCase) activity in peripheral blood cells combined with mutation analysis at the DNA level of the glucocerebrosidase gene (*GBA1*), performed by whole-gene sequence [15].

Work up panel tests:

Enzyme Activity

Diagnosis is confirmed through measurement of glucocerebrosidase activity in peripheral blood leukocytes. Less than 15% of mean normal activity is diagnostic.

Molecular diagnosis:

It is complicated by the presence of recombinant alleles originating from a highly homologous pseudogene. Clinical exome sequencing (CES) is a rapid genetic approach for identifying disease-causing mutations. However, copy number variation and recombination events are poorly detected, and further investigations are required to avoid mis-genotyping [16].

Associated Marker Testing

Glucosylsphingosine (Lyso-Gb1), has been confirmed to be a good marker for confirming the diagnosis and monitoring the response to therapy[17]. Many plasma biomarkers have been used such as angiotensin-converting enzyme, ferritin, alkaline phosphatase, and high-density lipoprotein) were used to diagnose and follow up patients with GD; but they are not used and more as they are not specific[18, 19]. Use of chitotriosidase and chemokine (C-C motif) ligand 18 (CCL18), as biomarkers are also limited, as they are not specific for GD [20].

Imaging

- Ultrasonography - may reveal abdominal organomegaly.
- MRI - may be useful in revealing early skeletal involvement (avascular necrosis, spinal degradation, and degree of bone marrow infiltration.
- Radiography - may reveal skeletal manifestations and pulmonary involvement.
- Dual-energy x-ray absorptiometry - may evaluate osteopenia and bone crises.
- Echocardiography is helpful in evaluating the possibility of pulmonary hypertension.
- In neuronopathic Gaucher disease, monitoring of electroencephalogram (EEG), brainstem-evoked potential, swallowing studies, and neuro-ophthalmologic evaluation should be done at regular intervals.

Bone Marrow Aspiration

This invasive procedure; used to detect the pathognomonic Gaucher cells is not acceptable any more. It can be done only if other hematologic comorbid conditions are suspected. [21]

Liver Biopsy

- It shows Gaucher cells in the sinusoids, but the hepatocytes are not affected: this explains the low incidence of liver failure in patients with Gaucher disease.
- It may be performed to evaluate unexplained hepatomegaly. However, a biopsy is rarely needed because a specific diagnostic test is available.

Prenatal Diagnosis

Prenatal diagnosis of GD can be performed by genetic analysis, using either chorionic villus sampling (sampled at 10–12 weeks of amenorrhea) or amniotic fluid cells (as early as 16 weeks of amenorrhea), but only if the index case genotype has been previously identified [22].

It can also be done by measuring glucocerebrosidase activity on fresh chorionic villi or cultured amniotic cells[23].

Neonatal screening

Neonatal screening for GD is possible now and can be easily performed using dried blood spot (DBS) sample using a heel-prick procedure 4 days after birth. This simple technique is easy to be done and transported via regular mail. It just has some limitations concerning measuring GCase activity It was strongly suggested that early screening and diagnosis may have a very significant impact on the quality of life and potentially longevity in infants with GD [24].

Gaucher disease biomarkers:

Currently, the most interesting biomarkers are chitotriosidase, CCL18, glucosylsphingosine and ferritin. Chitotriosidase is produced in large quantities by Gaucher cells, and it has been used as a biomarker since 1994 [25]
Its level is generally very high without treatment, so it can be used to monitor treatment efficacy and is considered to have some prognostic value [26]. Ferritinemia is higher than normal in most GD patients (>85%), while serum iron, transferrin saturation and soluble transferrin receptor concentrations remain normal [27].

Management:

Treatment for Gaucher disease falls into two categories, enzyme replacement therapy (ERT), and substrate reduction therapy (SRT) [28]. The FDA has approved both Cerezyme (imiglucerase) and VPRIV (velaglucerase alfa) for Gaucher disease type 1 and 3 enzyme replacement therapy [29]. Enzyme replacement therapy does not correct the underlying genetic defect and acts only to relieve signs, symptoms, and ongoing damage caused by the accumulation of toxins. Enzyme replacement therapy can improve the non-neurological signs and symptoms associated with type 3 Gaucher disease, as it reducing hepatosplenomegaly and hematological signs, frequently alleviate skeletal manifestations of GD, promote catch-up growth in children and improve health-related quality of life. However, it classically cannot change an enzyme deficient in the brain as it cannot cross the blood-brain barrier and consequently it is not effective to treat the neurological problems associated with type 2 and 3 Gaucher disease. Three non-bioidentical ERT products are commercially available: imiglucerase, velaglucerase alfa, and taliglucerase alfa [30]. Substrate reduction therapy is an orally administered small-molecule. In the case of Gaucher disease, the goal is to use substrate reduction therapies that can inhibit the first committed step in glycosphingolipid biosynthesis. There are two FDA-approved substrate reduction therapy drugs to treat patients with GD; eliglustat and miglustat. Eliglustat, a glucosylceramide synthase inhibitor, does not effectively cross the blood-brain barrier is indicated only for type 1 Gaucher disease. [31,32] [33]. Miglustat can cross the blood-brain barrier and could, therefore, be potentially beneficial for type 2 and 3 Gaucher disease. Nevertheless, miglustat is currently indicated only for the treatment of mild to moderate type 1 Gaucher disease only in adults. Though, its efficacy is limited by its relatively low inhibitory effect on glucosylceramide synthase at doses that are not associated with unacceptable side effects that include diarrhea, weight loss, tremors, and paresthesia [34,35].

Symptomatic Treatment

In addition to ERT or SRT, other management options are used either alone, or together with ERT or SRT to improve precise disease symptoms such as bone disease, hepatosplenomegaly, bleeding, pulmonary hypertension and Parkinsonism[36]. In the era of enzyme replacement therapy, splenectomy should be avoided in GD patients. Splenectomy should only be performed in exceptional circumstances and considered only in rare cases of non-response to well conducted ERT with persistent severe cytopenia or in cases of splenic rupture. In severe thrombocytopenia or symptomatic organomegaly unresponsive to ERT, splenectomy might be performed. Defects in coagulation, and non-corrected thrombocytopenia pathways may cause increased bleeding risk in GD patients and require constant monitoring. [37, 38]. Bone disease usually specifies progressive stages of GD, but patients' susceptibility to fractures, osteopenia, and osteonecrosis can also be a sign of GD in asymptomatic patients [38]. Painful bone crises often require temporary immobilization and use of strong analgesics. Specific treatment typically reduces the frequency and intensity of these crises [39]. Specific therapy remains the best treatment for GD-related osteopenia and osteoporosis. Bisphosphonates are nonetheless often indicated in cases of persistent osteoporosis, especially in postmenopausal women [40]. Orthopedic surgical interventions may be necessary for linked bone complications and pathological fractures. Liver transplantation is used infrequently and reserved for patients without neurological involvement. Previously, the youngest patient identified in the literature is an 11-year-old with GD1 who underwent LT and died shortly after due to severe rejection [41]. Psychological support should be routinely offered to GD patients and they should be put in touch with patients' associations.

Follow up and monitoring

Patient monitoring parameters include regular clinical, biological and radiological evaluations. Biomarker levels (chitotriosidase, CCL18 and ferritin) decrease relatively quickly with ERT, prior to the normalization of platelet and hemoglobin levels [42] . Hepatosplenomegaly decreases more slowly, frequently over a period of two years. Improvement of bone abnormalities is usually observed after 2–4 years of treatment, but some abnormalities continue irreversible (hepatic or splenic fibrosis, and bone infarction sequelae). A significant proportion of patients show improvement, but without normalization of their cytopenia or organomegaly [43]. GD3 patients require additional neurological monitoring. Pediatric patients are

monitored more frequently: a full clinical and laboratory assessment in addition to imaging procedures must be carried out every six months to follow up the disease progression.

Prognosis

At present, existing treatments make it possible to considerably improve the quality of life of the patients. Outcomes may be unfavorable due to aggressive, irreversible and disabling bone disease, despite specific treatment as bone complications can occur in spite of treatment in some patients; due to the onset of Parkinson's disease and Lewy body dementia; or the occurrence of a blood disease or cancer (hepatocellular carcinoma). When ERT is ineffective in patients with GD3, progressive neurological deterioration has an impact on their prognosis. Moreover, GD3 patients can die suddenly [44]. The outcome is always fatal for patients with type 2 GD.

Conclusions and recommendations

Although it is the most common of the lysosomal storage diseases, Gaucher disease remains rare and most cases present a gradual onset phenotype, which explains its delayed diagnosis. It is important to include GD in the differential diagnosis of all cases of splenomegaly and thrombocytopenia, Significant new insights into GD's pathophysiology show that G disease cases has a much broader impact than the simple macrophage load that transforms them into Gaucher cells. These insights will open new pathways for the development of innovative therapeutic strategies. Eventually, drugs that can modify the neurological phenotype are expected to be developed. It is likely that more complex molecular studies will ultimately contribute to customized patient management.

The recent therapeutic advances such as development of new enzymes and a new substrate inhibitor enabled a significant progress in GD management.Patients with GD, including asymptomatic patients, must be monitored regularly to detect any complications due to progression of the disease.

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