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Gaucher Disease and Reproduction

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Abstract

Gaucher disease is a rare autosomal recessive disorder characterized by the defective function of the catabolic enzyme -glucocerebrosidase causing accumulation of its substrate, glucocerebroside in the macrophages resulting into the hematological, visceral, bone and neurologic system deformities. The clinical signs and symptoms are neurological dysfunctions, bone infarcts and malformations, hepatosplenomegaly, and hypersplenism causing anemia, neutropenia, and thrombocytopenia. Gaucher disease is classified into three broad phenotypes based upon the presence or absence of neurological involvement and classified into type 1, 2, and 3. Disease-specific treatment consists of intravenous enzyme replacement therapy (ERT) using one of the currently available molecules (imiglucerase, velaglucerase, or taliglucerase). Orally administered inhibitors of glucosylceramide biosynthesis can also be used (miglustat or eliglustat). A diagnosis of GD can be confirmed by demonstrating the deficiency of acid glucocerebrosidase activity in leukocytes. Mutations in the GBA1 gene should be identified as they may be of prognostic value in some cases. Patients with type-1 GD carry GBA1 mutation. These patients are more predisposed to develop Parkinson's disease, and the risk of neoplasia. In this review we have provided a short description of Gaucher disease, its subtypes, important mutations involved, and a brief overview of how Gaucher disease affects the outcome of pregnancy. Gaucher disease in pregnancy is an important area to be analyzed in depth, as patients undergoing pregnancy may have additional risk of developing anemia thrombocytopenia etc., that may lead to the postpartum bleeding.

Keywords: Gaucher disease; Neuronopathic; Genetic testing glucocerebrosidase gene (GBA1); Gene therapy; Reproduction

Abbreviations: GD: Gaucher Disease; ERT: Enzyme Replacement Therapy; GBA1: Genetic Testing Glucocerebrosidase Gene; SRT: Substrate Reduction Therapy; APPT: Activated Partial Thromboplastin Time

Introduction

Gaucher disease (GD) is one of the most frequent glycolipid storage disorders caused due to the inherited deficiency of the lysosomal enzyme-glucocerebrosidase, resulting the increase of the substrate glucocerebroside in the cells of the macrophage-monocyte system. Key features of the disease are splenomegaly with hypersplenism, hepatomegaly and bone involvement. It is a single-gene disorder with phenotypic expression that is highly variable, ranging from asymptomatic (identified either through molecular analysis or enzyme deficiency) or lethal type that occur in the form of hydrops fetalis and ichthyosis, neurologic comorbidities (peripheral neuropathy and Parkinsonism), calcification of cardiac valves and pulmonary hypertension, most patients will present or develop signs/symptoms that are commonly managed by hematologists, for example, anemia, thrombocytopenia, and splenomegaly. Gaucher disease can be used as a model for other lysosomal storage diseases.

Presently because of advancement in the mutational detection for Gaucher disease, carrier screening has been incorporated into different ethnicities' [1]. Fortunately, now a days safe and effective replacement therapy, and substrate reduction therapy (SRT) [2] and other treatment modalities are available. This disease shows high degree of phenotype heterozygosity. There are >300 mutations known since the glucocerebrosidase gene was cloned partly [3,4,5]. Several private mutations are also known that may be either single or combined mutations, whole genome sequencing is recommended for accurate genotyping.

Gaucher disease (OMIM#606463) is one of the common autosomal recessive lysosomal storage diseases [6]. It was first reported by Philippe Gaucher in 1882. It is seen in three broad phenotypes (type I, II and III) depending upon the presence or absence of neurological involvement. Type II and III were discovered in 1927 and 1959 [7]. Lot of variation is seen, among Gaucher disease patients, some are asymptomatic; others show severe, and chronic complications [8]. In (Table 1) the characteristic features of all the three types of Gaucher disease are summarized.

Table 1: Types of Gaucher Disease.

	Type 1: Non Neuronopathic (Adult)	Type 2: Acute Neuronopathic (Infantile)	Type 3: Chronic/ Subacute Neuronopathic (Juvenile)
Affected groups	Young adults/adults Most common in Ashkenazi Jewish population (1 in 450) 1 in 100,000 general population	Infants (rarely) No particular ethnicity 1 in 100,000 live births	Children/young adults No particular ethnicity 1 in 50,000 live births Norrbottnian variant: Sweden, until early adulthood
Distinguishing Symptom	Liver, spleen, and bone No nervous system problems	Early nervous system problems Brainstem abnormalities	Later onset of nervous system problems: incoordination, mental deterioration, myoclonic seizures
Effects of disease	Varies from mild to severe	Death in infancy (age <2 years)	Slowly progressive – becomes severe later in childhood
Glucocerebrosidase Activity	Some activity, but much less than Normal	Very little activity	Little activity

Gaucher disease is a multi-systemic chronic disease involving liver, spleen, bone marrow and lymph nodes. Familial segregation is often seen. It is an autosomal recessive disorder that is caused by the deficiency in glucocerebrosidase, a lysosomal hydrolase is involved in the stepwise degradation of complex glycosphingolipids or in few cases by a deficiency in the activator protein Sarposin-C is responsible for this defect [9]. As a result, the glucocerebrosidase, gets accumulated in the monocyte-macrophage system [10,11] resulting macrophages to get distended with the substrates leading to the typical appearance of Gaucher cells [12]. The Gaucher cells are very large cells with a diameter of 20-80µm, round or polyhedral. Gaucher cells have small, usually eccentrically placed nuclei and cytoplasm with characteristic wrinkles or striations. Electron microscopy reveals that the cytoplasm contains spindle or rod-shaped membrane-bound inclusion bodies of 0.6-4µm in diameter consisting of numerous small tubules of 13-75nm in diameter.

Laboratory Investigations

Various laboratory investigations are helpful in the diagnosis of the Gaucher disease. These are hematological investigations like platelet counts, prolonged prothrombin time and activated partial thromboplastin time (APPT).

Type-I Gaucher Disease

Type- I (GD, OMIM #230800, ORPHA355) is non-neuropathic most common form of the disease. This shows pan ethnicity with an estimated incidence of about 0.4 and 5.8/100,000 inhabitants. The incidence of type I GD is quite high among individuals belonging to Ashkenazi Jewish ancestry. Diagnosis can be made by measuring acid -glucosidase activity in peripheral blood leukocytes or fibroblast cultures. However, final diagnosis depends upon the molecular testing of GBA gene sequencing. A recent study on Jewish population revealed that in a larger population of Ashkenazi Jewish patients, the most common mutations are 1226G and 84GG accounted for 90.4% of the mutations. Beutler et.al. have reported three public mutations increasing the Gaucher mutation incidence to 97.5% [6]. There is some data available on Netherland, Portugal, and Australia among reproductive age group population. It is 2 per 100,000 live births among Netherland. Among Portugal 3 per 100,000 live births and among Australia 1 per 57,000 live births [13, 14].

In Type-I Gaucher disease the spinal cord and brain are usually not involved hence patients with this disorder can live for several years. These patients show hepatosplenomegaly, splenomegaly, anemia, thrombocytopenia, osteopenia, focal lytic or sclerotic lesions, osteonecrosis and portal hypertension [15]. They may show pulmonary involvement. It has been reported that type 1 GD is associated with an increased risk of certain malignancies, especially multiple myeloma [16]. These symptoms reveal high degree of variability. The important clinical symptoms are enlargement of the liver and spleen (hepatosplenomegaly), a low number of red blood cells (anemia), easy bruising caused by a decrease in blood platelets (thrombocytopenia), chronic fatigue is common (50% of patients) and often has an impact on school life or socio-professional activities. These patients may suffer from children growth retardation and delayed puberty are common, lung disease, and bone disease such as bone pain, fractures, and arthritis. People with GD1 may be at increased risk for Parkinson disease, peripheral neuropathy, certain cancers, and osteoporosis [17].

Type-II Gaucher disease

The incidence of Type II GD, least common form of GD occurring with less than one in 100,000 individuals. Nagral et al. [18] have conducted a survey to evaluate the awareness of Gaucher disease (GD), with epidemiology to accurately depict the total societal burden of this rare worldwide disorder. They have taken into consideration, 188 full-text articles and have shown that birth incidence of GD in the general population varied from 0.39 to 5.80 per 100 000, and prevalence ranged from 0.70 to 1.75 per 100 000, respectively. Time from onset of GD symptoms

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to clinical diagnosis was highly variable, with median delay up to 7 years [18]. The prevalence of type-II GD is approximately 1/100,000. Mostly patients suffer from hydrops fetalis. Other clinical manifestations are skin abnormalities [10,19] that may be due to altered ratios of ceramides to glucosylceramides in the outermost layers of skin [17]. These patients also suffer from hepatosplenomegaly, thrombocytopenia, anemia, dysmorphology and various neurological involvements.

The first signs are oculomotor paralysis or bilateral fixed strabismus associated with bulbar signs, in particular severe swallowing difficulties, progressive spasticity, and dystonic movements. Seizures occur later and manifest as myoclonic epilepsy that is refractory to treatment with anti-epileptics. In type-II Gaucher disease mutation is present in the *GBA* gene (1q21) that codes for the lysosomal enzyme, glucocerebrosidase. The deficiency in glucocerebrosidase leads to the accumulation of glucosylceramidase (or beta-glucocerebrosidase) deposits in the cells of the reticuloendothelial system of the liver, of the spleen and the bone marrow (Gaucher cells). These patients can be diagnosed by using antenatal diagnosis by measuring enzyme activity in the chorionic villus sample at 10-12 weeks of pregnancy or amniocytes in culture towards 16 weeks of pregnancy. The deasease is transmitted in an autosomal recessive manner. The patient suffering from type 2 gaucher disease dye before the age of two years. The management of patients with Type-2 Gaucher disease is quite challenging. Different clinical features need to be evaluated systematically. The management of common clinical features of type 2 gaucher disease is shown in (Table 2).

Table 2: Managing common clinical features of Type 2 Gaucher Disease.

Clinical feature	Recommended evaluation	Management
Feeding difficulties and failure to thrive	Examine by a speech pathologist Video fluoroscopy to assess swallowing and aspirations Nutrition assessment	
	Clinical diagnosis can be demonstrated on video fluoroscopy and pH meter	Head elevation
	Consider ENT evaluation	Treat GE reflux
	Neurologic evaluation	Consider benzodiazepines Consider EEG
Irritability	Nutrition assessment of intake	Provide sufficient macro- and micronutrients Gentle handling and maintenance of a calm and familiar environment Consider benzodiazepines
Fever	Evaluate for infection / recurrent aspirations	Antipyretics Consider empiric antibiotic treatment
Lung disease	Monitor for oxygen desaturations / respiratory distress on physical exam Chest X ray for evaluation of disease progression and pulmonary infections Video fluoroscopy for evaluation of aspirations Consider Pulmonology evaluation	Treat GE reflux Consider strict enteral feeding Treat pulmonary infections Oxygen
Visceromegaly	Monitor CBC	Enzyme replacement therapy is generally not indicated
Bleeding diasthesis	Check CBC, PT/PTT Check liver function tests Consider testing coagulation factors	Vitamin K Consider transfusion of platelets / fresh frozen plasma

Type-III Gaucher Diseases

Type-III Gaucher disease [OMIM# 2301000] (sub-acute neuronopathic) involves central nervous system causing abnormal eye movements, seizures, and brain damage. Type-3 occurs during infancy while patients with type–III patho-gnomonic neurologic symptoms may be subtle and develop at late stages [20] and are affected in much latter age group. Lethal form is known as perinatal lethal form may show extensive swelling due to fluid accumulation before birth resulting into hydrops fetalis; dry, scaly skin (ichthyosis) or other skin abnormalities; hepatosplenomegaly; characteristic facial features; and other neurological problems. These patients can survive only for few days after birth. Type 3 GD (GD3) is found in 5% of overall patients. It is mostly reported from Northern Europe, Egypt and East Asia [21] a high incidence of GD3 is found in the Swedish province of Norrbotten and is therefore also referred to as the Norrbottnian type of GD [22].

The genotype- phenotype correlation among three different forms of Gaucher disease is poorly understood.There are many other names for this disease like cerebrosidelipidosis syndrome, Gauchersplenomegaly, Gaucher syndrome, Gaucher disease, Gaucher disease glucocerebrosidase deficiency, glucocerebrosidosis, glucosylcerebroside lipidosisglucosylceramidase deficiency, glucosylceramide beta-glucosidasedeficiency, glucosylceramidelipidosis, kerasinhistiocytosis, kerasinlipoidosis, kerasinthesaurismosis, lipoid histiocytosis (kerasin type)[23].

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GBA1 Mutations

The gene (GBA1) is located on the long arm of chromosome 1 (1q21) having 11 exons. Interestingly a highly homologous pseudogene (GBAP) is also situated on the same locus, but it is (16 kb downstream) and is responsible for the recombination events between GBAP and GBA1 (e.g., RecNciI allele) [24]. More than 400 mutations have been described in the GBA1 gene, some of them are more common, such as c.1226A>G (N370S), c.1448T>C (L444P), c.84dup, c.115+1G>A (IVS2+1G>A) and RecNciI [25]. The patients of Gaucher disease with Ashkenazi Jewish origin reveal c.1226A>G, c.84dup, c.1448T>C and c.115+1G>A. The c.1226A>G (N370S) mutation is rarely seen in Asian and Arab populations. The presence of the c.1226A>G (N370S) mutation in a homozygous or heterozygous state excludes the risk of neurological involvement. Patients homozygous for the N370S mutation can remain asymptomatic for a very long time, whereas those homozygous for the L444P mutation are at a high risk of developing neurological impairment (GD2 or GD3). Thepatients homozygotes for the rare c.1342G>C (D409H) mutation show characteristic heart valve damage [26].

The Gaucher patients carrying two null mutations (leading to a total absence of glucocerebrosidase activity) do not survive beyond the perinatal period [22]. The presence of the c.1226A>G (N370S) mutation in a homozygous or heterozygous state eliminates the risk of neurological involvement (GD2 or GD3), but it does not predict the severity of bone and visceral involvement. Patients homozygous for the N370S mutation can remain asymptomatic for a long time, whereas homozygous for the L444P mutation are at a high risk for developing neurological impairment (GD2 or GD3). Homozygotes for the rare c.1342G>C (D409H) mutation show heart valve damage [24]. Sidranky has described that patient carrying two null mutations (leading to a total absence of glucocerebrosidase activity) do not survive long (fetal forms incompatible with life) [4,27].

Mutations in the GBA gene diminish or eradicate the activity of beta-glucocerebrosidase hence less production of glucocerebroside resulting into the formation of toxicity within cells. The abnormal accumulation and storage of these substances results into Gaucher disease. Various SNPs are also associated with type 1, 2 or 3 Gaucher disease [5]. These are Asn370Ser (also known as N370S) is associated with type I non-neuropathic) disease, rs421016 and rs35095275 are related with types II and III, Arg463Cys is concomitant with types II and III, rs104886460, also known as IVS2+1G-A. Some of the genotypes increase the risk of Parkinson disease these are rs76763715 or i4000415, also known as N370S (risk genotype CC), rs387906315 or i4000417, also known as 84GG (risk genotype GG), rs80356773 or i4000386, also known as R496H (risk genotype AA), rs80356769 or i4000419, also known as V394L (risk genotype AA). All the three types are highly heterogeneous in nature. A recent study has shown 14 novel variants in GNB1 including 10 mis-sense changes which were assessed for trimeric G protein complex formation and signaling by BRET-based cellular assays to characterize their functional impact [28].

Genotype/Phenotype Correlation

It is generally difficult to predict disease progression in GD based on the *GBA1* genotype. The nomenclature for each amino acid changes encountered in *GBA1* has recently been revised to take into consideration the 39 amino acid leader sequence. It is evident that there are numerous genotypes and clinical phenotypes associated with Type 2 GD. However, certain generalizations can be made based on these data, notably the absence of one of the most common *GBA1* mutations, Asn370Ser (Asn409Ser). Patients heterozygous or homozygous for this mutation do not manifest Type 2 GD. There has, however, been at least one report where Asn370Ser (Asn409Ser) was found on the same allele in cis with another *GBA1* mutation, which can further confuse the picture. In contrast, the mutation Leu444Pro (Leu483Pro) is frequently encountered in Type 2 GD, although it is rare to identify patients who are homozygous. When homozygosity for this mutation is reported in patients with Type 2 GD, further evaluation often shows that at least one Leu444Pro (Leu483Pro) allele is part of a recombinant allele with other mutations.

Such alleles are null alleles, and homozygosity results in early lethality. Other null alleles like c.84insG or IVS2+1 is also found in Type 2 GD, often with a Leu444Pro (Leu483Pro) mutation on the second allele. Mutations involving an arginine such as Arg257Gly (Arg286Gly), Arg285His (Arg324His), Arg131Leu (Arg170Leu), Arg120Try (Arg159Try), Arg359X (Arg398X), and Arg463His (Arg463His) appear to be frequent. One allele with two GBA1 mutations, D409H+H255Q (Asp448His+His294Gln), is often found among patients with Type 2 GD of Greek or Albanian ancestry [29,30]. A relatively frequent *GBA1* polymorphism E326K (E365K) is found in roughly 2-4% of the population and can also be encountered among patients with Type 2 GD along with a second *GBA1* mutation on the same allele. *GBA1* gene mutations results in the less GCase activity resulting into the accumulation of the GCase substrate, GlcCer, in macrophages, get transformed into Gaucher cells, visible through electron microscope.

The monocyte/ macrophage lineage eradicateerythroid and leukocytes, containing glycosphingolipids. This is the source of GlcCer. If GlcCer is increased in Gaucher cells affecting the bones. The neurological contribution is less explained however, GlcCer turnover in neurons is low resulting into less GCase activity [31]. However, in a fly model neuronopathic GD demonstrated autophagy due to the impairment in the GCase-deficient fly brains [32]. Mutation in the PSAP gene, leads to the deficiency in saposin C without GCase deficiency. These patients are mostly present with neurological features like type-3 GD [33]. A recent study by Paskulin et. al. [34] have suggested that a rare *GBA1* genotype is associated with severe bone disease among Gaucher patients. This is the first GD family with the E349K/S366N *GBA1* genotype which is associated with severe bone disease and mild visceral and

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hematological manifestations. More genotype-phenotype studies are needed to fully establish a causational relationship between this and other rare genotype and the patients' unique phenotype [34].

There is a close by pseudogene showing 96% homology with *GBA1* in the coding regions, genotyping is quite- challenging as several mutations originate from the pseudogene sequence, and it is essential to distinguish two sequences. Most of the mutations are rare or private point mutations, insertions, deletions or splice-site changes, unfortunately normal screening may not detect most of the cases. Interestingly some of the mutations might have arisen because of a recombination event that occurred between *GBA1* and its homologous nearby pseudogene and are referred to as recombinant alleles. These alleles are seen among infants with Type 2 GD. Recombinant alleles may cause the introduction of more than one alteration on the same allele hence the entire sequence should be carefully analyzed. Generally, the enzyme assay is not reliable for heterozygote hence molecular methods should be used especially in families where the *GBA1* mutations are known. Patients with Type 2 GD exhibit epidermal abnormalities regardless of whether ichthyosis is clinically evident or not. This finding may have potential diagnostic importance.

On electron microscopy, the skin ultrastructure reveals immature partially processed lamellar bilayers. A study comparing 20 cases with Type 2 GD to other forms of GD demonstrated that these alterations were unique to Type 2 GD and could help to differentiate between patients with Type 2 versus Type 3 GD. However, such evaluations are currently performed for research only [35]. While it is not a recommended method for diagnosis, many affected infants have been identified because of pathologic evaluations of biopsy specimen. The classic finding in bone marrow biopsies or liver, lung, and spleen samples is the presence of Gaucher cells, lipid engorged macrophages with a "wrinkled tissue" appearance of the cytoplasm. However, enzymatic or DNA confirmation is essential, as storage cells resembling Gaucher cells can be found in other conditions. Clinicians should consider a diagnosis of GD in newborns with hepatosplenomegaly, hematological abnormalities, developmental delay, and failure to thrive.

Diagnosis of Gaucher disease

Gaucher disease can be diagnosed by examining the G Case activity in total leukocytes or mononuclear cells, or cultured fibroblasts. The residual enzyme activity is usually approximately 10-15% of the normal value. Under rare circumstances G Case activity is normal but the clinical symptoms and other biomarkers are suggestive of GD. In this case the very rare saposin C deficiency should be tested. In case chitotriosidase activity is very high then saposin C deficiency should be examined. The diagnosis is made by PSAP gene sequencing. Vary rarely bone marrow aspirations are helpful when patients without a diagnosis with isolated thrombocytopenia and/or splenomegaly are found with the presence of gaucher cells.

However, this test need to be seen with caution as many times Gaucher like pseudo Gaucher cells are present in some blood disorders or infectious diseases, such as myeloma with histiocytic accumulation of immunoglobulin crystals [30], waldenstrom's disease and other lymphomas with monoclonal gammopathy [36], chronic myeloid leukemia or myelodysplasia [24,37], or atypical mycobacteria [38]. Best confirmation is possible by carrying out the mutation analysis. Prenatal diagnosis should be carried out using mutation analysis in high- risk patients. Some of the biomarkers have been used to diagnose GD patients but due to lack of specificity these are not in frequent use. Some of the routine investigations like liver function test, C Reactive Protein (CRP), Serum calcium and auto antibodies should be carried out. Radiological testing is also essential for GD patients [5].

Treatment of Gaucher disease

Treatment of Gaucher disease is quite expensive. One of the most common treatment modalities is enzyme replacement therapy (ERT). Both enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) are FDA approved drugs. It is recommended that only symptomatic patients of GD 1 and GD 3 merit treatment as it helps in reducing the liver and spleen size, bone symptoms and improves the blood counts. Type-I is milder form and treatable. Enzyme replacement therapy (ERT) ERT [39]; bone pain improves, there are fewer bone crises [40], and occurrences of skeletal events are decrease [41], although ERT does not completely eradicate them. Early treatment with ERT reveals better improvement the risk of AVN is decreased [42]. None of the ERTs are indicated for GD2 as treatment has no impact on the rapid progression of its severe neurological symptoms [43,44]. There is no evidence that ERT has reversed, stabilized, or slowed the progression of neurological involvement. In some cases, allergies are also associated with ERT specially with taliglucerase.

During pregnancy ERT can be used it is not associated with any fetal malformations [45]. It has been shown that substrate reduction therapy (SRT) reduces excess cell GlcCer. Miglustation is a second-line treatment to be used when ERT is no longer accepted by the patient or cannot be used due to intolerance. However, it should not be used during pregnancy. Miglustat crosses the blood brain barrier but show no neurological symptoms in GD3. Another substrate inhibitor, eliglustat (Cerdelga®, Sanofi-Genzyme) has been approved in 2015. It is orally administered and act as a GlcCer synthase inhibitor, but is more specific and more potent than miglustat, because it is an analogue of the ceramide part [46-49]. It is recommended that CYP2D6 genotyping should be done before the drug is being used [50].

Eliglustat is indicated for the long-term treatment of adults with GD1 who are cytochrome 2D6-poor are, intermediate or extensive metabolizers. It is not indicated for use in ultra-extensive

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metabolizers. Eliglustat is not recommended in patients with pre-existing cardiac disease (e.g., congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia, long QTsyndrome), and in concomitant use with Class 1A and Class III antiarrhythmics. Adverse effects are uncommon and usually mild, including headache and pain in limb extremities in less than 10% of the cases. Given that it is metabolized by cytochrome P450, certain drug–drug interactions are anticipated. Eliglustat offers eligible patients a daily oral therapy alternative to biweekly infusions of ERT.

Specific Treatments

Bone marrow transplantation can cure patients with GD [51], however, cost benefit analysis has revealed that BMT is not cost-effective treatment. Full engraftment of a hematopoietic stem cell transplantation (HSCT) has been performed in patients with Type 1 GD resulting in complete hematologic correction [52, 53]. Aflaki et al. described four Swedish patients with Type 3 GD who underwent bone marrow transplantation between the ages of 2-9 years old [54]. Two patients had no cognitive decline even after ten years. However, both developed epilepsy at 14 and 22 years after allo-HSCT [55]. Thus, the procedure does not prevent development of neurological damage although it might affect the extent or rate of neurological deterioration. Published reports regarding the results of bone marrow transplantation in patients with Type 2GD are not available. The risks involved in transplanting a seriously ill infant must be seriously considered, given the strong possibility of continued neurological deterioration. Moreover, end-of-life issues may need to be addressed in distant centers, away from the support of home and family.

Clinical Management of Gaucher disease

Most patients with type I Gaucher disease require splenectomy which manages thrombocytopenia and anemia; however, splenectomy increases in bone involvement resulting into osteolytic lesions [56] to avoid this partial splenectomy can be performed. There are reports suggesting gene therapy [57-59]. Enzyme replacement therapy is the standard protocol for the treatment where weekly intravenous infusions of macrophage-targeted human placental glucocerebrosidase revealed clinical improvement in a patient with type I Gaucher disease. Sequential deglycosylation of the oligosaccharide chains of the native enzyme were used to yield a mannose-terminated preparation that is specifically bound by lectin on the membrane of macrophages.

Substrate 1 Reduction Therapy

Pastores et al. reported results from treatment with N-butyldeoxynojirimycin (NB-DNJ; Miglustat), an inhibitor of glucosylceramide synthase (UGCG; 602874), in 10 adult patients with type I Gaucher disease. Treatment over 24 months resulted in decreased liver and spleen volumes and clinical improvement. Bone involvement and platelet and hemoglobin levels remained stable, and the treatment was well tolerated [60,61].

Chaperone therapy

Restoration of the mutant enzyme activity by small molecule compounds (chaperones) capable of crossing the blood-brain barrier is a new approach to treat LSDs [61,62]. Currently, there is an effort to identify candidate molecules [63,64]. However, this treatment will be helpful only for mutations in *GBA1* that result in an unstable mutant protein and may not be appropriate for patients with null alleles. Induced pluripotent stem cells (iPSCs) generated from fibroblasts of patients with type 2 GD may facilitate studies of candidate molecules. Gaucher iPSC lines show deficient GCase and were differentiated into macrophages that exhibit substrate accumulation [65]. This GD phenotype in macrophages was successfully reversed with a new molecular chaperone [54].

Gene therapy

Gene therapy is a potentially promising future therapeutic strategy for genetic diseases with enzymatic deficiencies like GD [55], although the effectiveness of gene therapy in CNS disease is not clear. Intracerebral injection of the vector carrying the wild-type gene may be a possible strategy.

Additional treatment targets

As we advance our understanding of the mechanisms involved in neurodegeneration, other potential targets will likely be identified. Insights from basic science research like the potential role RIPK3 may provide new leads for future drug development.

Counseling Parents and Palliative Care

Facing the diagnosis of Type 2 GD in an infant is extremely difficult and can be emotionally overwhelming for parents, caregivers, and health care providers. In many cases, the child appears normal at birth and during the first months of life until rapid deterioration begins. During these circumstances, parents and clinicians should work together to make important and complex decisions about the child's medical care. These decisions are based on a variety of considerations including medical information, values, cultural expectations, economic considerations, and parental beliefs [56]. Studies have shown that parents of critically ill children need sensitivity, empathy, follow-up contact and information about counseling from healthcare providers [66]. This combination of education, support, and empathy can best be achieved by a multidisciplinary approach. Patient support groups or on-line chat rooms can also be helpful to some parents.

Potential Future Therapies

Substrate reduction therapy

Inhibitors of glucosylceramide synthase have been explored to attenuate glucosylceramide production and accumulation in various organs. The currently available therapy is not beneficial in neuropathic GD (Type 2 and 3) [67]. A novel glucosylceramide synthase inhibitor decreased substrate accumulation in the brains

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of a mouse model for neuronopathic GD [68]. This treatment modality might be beneficial for neuronopathic GD if given pre-symptomatically and before significant accumulation of substrate in the brain occurs, perhaps through newborn screening programs [69].

Gaucher Disease and Reproduction

Gaucher disease and reproduction needs a special attention as during reproductive pregnancy prevalence of Gaucher disease varies in different countries in Netherlands it is seen among 2 per 100,000 live births, in Australia 1 per 57,000 live births and Portugal 3 per100,000 live births [70]. The combination of Gaucher type I and pregnancy is known for more than 40 years. It was believed that there was an increased risk of maternal and fetal death. Thrombocytopenia and anemia are usually mild [71,72]. Although cirrhosis is an occasional problem, this may result in the portal hypertension [73], no fetal abnormalities due to maternal Gaucher's disease have been documented. Gaucher disease with pregnancy result in large number of complications like hematological parameters are disturbed, infections and postpartum bleeding and bone disease. It is also associated with the bleeding in the postpartum stage. Bleeding may be due to platelet aggregation. Sometime oocyte dysfunction, recurrent pregnancy loss, are also reported. Enzyme replacement therapy is the choice of treatment [74] [Table 3].

Table 3: Pregnancy and Gaucher disease.

No. of Pregnancies	Complications	No Treatment	Treatment received	Normal Outcome	Spontaneous abortion/ abnormal outcome	Elective abortion	Neonatal death or other complications	ERT received	Author/ year	Conclusion
453	No	336	117	312	12	11	1	117	Panahloo et.al. 2018 [102]	
Case report with two pregnancies	No				Developed Parkinson disease				Kilpatrick et.al. [91]	Family history of Gaucher disease, with INSV2 mutation,
15	no	Taliglucerase alfa	9	8	1 (missed abortion)	no	no	Taliglucerase alfa	Elstein et.al, [88]	Taliglucerase alfa safe drug during pregnancy
Case report with GB1	no	Imiglucerase	1	1	no	no	no	yes	Giannubilo et.al [92]	Imiglucerase effective drug
103			67 pt received no treatment,36 pt received imiglucerase	34/36	two/36, 13/67		two/67 ectopic pregnancy,21/67, bleeding,1/67 bone crisis	Imiglucerase	Martins et al 2015 [48]	Imiglucerase had favorable effects on the out come.
25 Singleton pregnancies		ERT	21 women received ERT treatment	21/4	2/Ist trimester abortion/1, missed abortion	no	nil	Velaglucerase alfa	Elstein, et.al [88]	ERT is safe

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Forty-five pregnancies of 20 women		ERT during pregnancy	6 women received ERT	31/45	14 women developed PPH	no	14/45	ERT	Simchen, MJ, [93]	Women with type 1 Gaucher disease who have abnormal platelet function tests may have an increased risk of PPH. platelet function tests may have an increased risk of PPH.
Case report	no	Imiglucerase	Case report	nil	A small amount of imiglucerase was found to be excreted into human breast milk, but only in the first milk produced after infusion	no		Imiglucerase	Sekijima,Y, [94]	Successful pregnancy and breast feeding in a Japanese patient with Gaucher disease.
19		ERT		nil	Successful pregnancy	no		ERT	Cohen Y, [95]	ERT for the benefit of all pregnant women with GD1, including mild GD1
Case report	no	ERT	Case report	nil	Successful pregnancy	no		ERT	Mamopoulos, A M [96]	Successful pregnancy
Review		ERT						ERT	Grabowski, G A [3]	Appropriate use of splenectomy and bisphosphonate treatment and biochemical markers
16		ERT	11 women/15 deliveries	5normal/2 vacume/1 placental extraction/8 cesarean sections	Mixed outcome	no		ERT	Ioscovich, A, [37]	ultidisciplinary approach is required to avoid postpartum hemorrhage, and preclude skeletal damage

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66 pregnancies (23 treated, 43 untreated)		ERT in 23 women, 43 women no treatment	Postpartum infections were prevalent among treated	3 spontaneous abortion in 1 treated women/	Varied results.			ERT	Elstein, Yonatan, [88]	more complications in treated group
Case report of two pregnancies		No ERT given to the patient		no complication in the pregnancy	No complications				Torloni, Maria Regina, [73]	Patient had two successful pregnancies with good perinatal results
Case report		ERT and conservative treatment	Successful pregnancy		Patient with Gaucher's disease and antiphospholipid antibodies				Sherer, Y, [97]	Patient on conservative treatment and on imiglucerase delivered normaly
Case report		Alglucerase enzyme replacement therapy	Successful pregnancy		Uncomplicated pregnancy				Aporta Rodriguez, R, [98]	Uncomplicated pregnancy
Case report		Blood transfusions			Hemorrhagic problems secondary to severe thrombocytopenia				Clarkson, C P, [99]	Patient developed disseminated intravascular coagulation and required transfusion of Eight 6-packs of platelets, 6 units of fresh frozen plasma, two 10-packs of cryoprecipitate, and 6 units of packed red blood cells.

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Review		Alglucerase is the treatment of choice	Alglucerase reduces the risk or not is not clear		Gaucher disease is associated with complications				Fasouliotis S.J, [72]	Gaucher's disease has several risks, including an increased severity of anemia and thrombocytopenia that can potentiate postpartum bleeding, and increased risk of infection and possibly An increased spontaneous abortion rate
6 cases	3 underwent repeated pregnancy loss.5 successful pregnancies	No ERT	Last pregnancy was terminated because of pulmonary hypertension	1/ pulmonary hypertension					Elstein, D, [71]	Pregnancy is not contraindicated (unless there is evidence or suspicion of pulmonary hypertension) and treatment should not be interrupted because the clinical improvement engendered by enzyme replacement therapy is conducive to fewer complications during pregnancy and delivery and post partum.

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Review	NA	ERT	Gaucher disease with pregnancy show complications like recurrent fetal loss						Rosnes JS et.al, [101]	Alglucerase reduces the risk of these complications during pregnancy and whether its use has any adverse effect on fetal development is still not clear.
53 Pregnancies	102 spontaneous pregnancies/9 pt had gaucher disease in 1st trimester		Gaucher disease lead to complications						Granovsky-Grisaru, [87]	Additional burden to female patients with Gaucher's disease.
47 Pregnancies of 17 women affected with Gaucher disease type-1	2 Spontaneous abortion/6pt required blood transfusion during preg.	No ERT	Complications seen during pregnancy in some women						Zlotogora, J, [102]	Appropriate follow-up should be planned at the beginning of pregnancy in these patients
Case report	3 Pregnancies	Ultrasound monitoring	No complication						Schoenfeld A, [103]	Ultrasound-monitoring is required

Immune mechanisms during pregnancy

Recently it has been reported that during pregnancy a systemic immunological adaptation takes place. There is a high degree of co-operation between fetus and maternal interactions instead of maternal immunosuppression during normal pregnancy. In Gaucher patients there exists an added risk during pregnancy as the immune system is deranged due to the activation of macrophages. It has been demonstrated that numerous cytokines, chemokines and other molecules-including IL-1β, IL-6, IL-8, TNFα (Tumor Necrosis Factor), M-CSF (Macrophage-Colony Stimulating Factor), MIP-1β, IL-18, IL-10, TGFβ, CCL-18, chitotriosidase, CD14s, and CD163s-are elevated in Gaucher patients' plasma and could be involved in hematological and bone complications [75-78]. Only some of these molecules are expressed by Gaucher cells themselves. In case of other specific disease biomarkers are chitotriosidase and CCL18 [75]. Osteoporosis may be linked to IL-10, which inhibits osteoblast activity, but also to IL-1β, IL-6 and M-CSF, MIP-1α and MIP-1β, that stimulate bone resorption by increasing osteoclast activity [79].

Other complications during pregnancy

Women with GD1 are at increased risk of complications during pregnancy, delivery, and the postpartum period [80]. Anemia and thrombocytopenia may worsen above and excessive bleeding may complicate pregnancy, delivery, and postpartum [81]. Hepatosplenomegaly may interfere with normal fetal growth. Increased calcium demand during pregnancy further increases

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the risk of bone crises, osteopenia, osteonecrosis, and fractures. In clinical practice, ERT is generally recommended before and during pregnancy to mitigate pregnancy-related risks, especially bleeding during delivery and postpartum [80,82,83]. Multiple studies and reviews have been published on the use of ERT during pregnancy [84,85]. Conversely, eliglustat is not approved for use in pregnancy due to lack of adequate or well-controlled studies in pregnant women [86]. The US Prescribing Information (PI) states that available data are not sufficient to assess drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes [86], and the EU SmPC states that, as a precautionary measure, it is recommended to avoid the use of eliglustat during pregnancy [87].

In 1960 people noted that there are more recurrent fetal losses in patients with Gaucher disease and it was thought that these patients may be sterilized or not opt for children [88]. In the following thirty years a series of publications presented good maternal and perinatal results, indicating that pregnancy did not exacerbate Gaucher's disease [72]. Based upon various case reports it has been suggested that patients with Gaucher disease should be well managed during pregnancy. There is an interesting case report where a case of Gaucher's disease with myocardial involvement n pregnancy was well managed [73]. There are some case reports available which suggest that autoimmune phenomena is present in these patients. Valizadeh in reported a 31-year-old female with splenomegaly and pancytopenia. She had developed left upper quadrant pain and fatigue for 9 months with significant exacerbation during pregnancy which ended to a living child. She had history of five pregnancies terminated with spontaneous abortions at 8-12 weeks. She had family history of anemia.

Peripheral blood smear showed red blood cells with hypochromia, a few target cells, and a few ovalocytes. Bone marrow aspiration revealed hypocellular marrow, cells containing "crinkled paper" cytoplasm, and glycolipid-laden macrophages. Hence, diagnosis of Gaucher's disease was made. Immunohistochemistry (IHC) on bone marrow biopsy of this patient demonstrated positive CD68 in all large cells, as well as positive lysozyme in all large cells compatible with Gaucher's disease. The enzymatic assay revealed the level of glucocerebrosidase to be 0.5μmol/1h (with reference range>4μmol/1h). She was also positive for antiphospholipid antibody. This case report suggested that patients with Gaucher disease with repeated pregnancy losses should be tested for antiphospholipid antibody [89]. Recently 453 cases with Gaucher disease were investigated for the outcome of pregnancy (336/453,74.2%). These women who did not receive GD-specific treatment during pregnancy, while enzyme replacement therapy (ERT) was received during 117/453 (25.8%) pregnancies.

No pregnancies exposed to substrate reduction therapy were reported. The percentage of normal outcomes (live birth delivered at term with no congenital abnormalities) was similar in untreated and treated pregnancies (92.9% vs. 91.4%). The percentage of spontaneous abortions in untreated pregnancies was 3.6% (95% CI, 1.9%-6.2%) compared with 6.9% (95% CI, 3.0%-13.1%) in treated pregnancies (p = 0.1866). In women who received velaglucerase alfa< 1 month prior to conception and/or during pregnancy, 34/36 (94.4%) pregnancies had normal outcomes and 2 (5.6%) ended in spontaneous abortion. Normal outcomes were observed in the 20 pregnancies with velaglucerase alfa exposure starting <1 month prior to conception and continuing through all trimesters. These observations, in addition to information in the literature, suggest that continuation of ERT during pregnancy may be appropriate for GD patients [90]. In table 3 we have summarized different studies with or without complications during pregnancy among Gaucher disease patients.

Most of the case reports have revealed no complication however they have received one or other kind of treatment and have revealed the importance of enzyme replacement therapy [86,90-102]. Recently an emphasis has been given on the prenatal diagnosis of Type-I Gaucher disease and replacement therapy [91, 103-105,106-108] and also emphasized the importance of genetic counseling during pregnancy. Parental feelings of guilt or blame can complicate the decision-making process as the child's condition deteriorates. Families need to be educated about risks and alternatives relevant to future family planning, including prenatal diagnosis, pre-implantation diagnosis, sperm, or egg donation, as well as adoption. In addition, the genetics team should be aware that unusual mechanisms including uniparental disomy for chromosome 1 and germline or de novo mutations have been described in patients with GD [109,110].

The importance of genetic counseling in Gaucher disease have been emphasized by Pastores and Hughes they have updated the review on Gaucher disease. Authors have suggested that pregnancy can exacerbate preexisting symptoms and trigger new features in affected women specially when they show severe thrombocytopenia and/or clotting abnormalities [111]. During pregnancy they are at increased risk for bleeding around the time of delivery. Evaluation by a hematologist prior to delivery has been recommended. The lack of studies on the safety of eliglustat use during pregnancy and lactation has led to the recommendation that this medication be avoided during pregnancy, if possible. Special emphasis has been recommended in case both pathogenic variants in a family are known – or assay of glucocerebrosidase enzymatic activity if only one or neither pathogenic variant in the family is known. Management of GD patients require a multidisciplinary approach.

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