The Clinical Management of Type 2 Gaucher Disease

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Abstract

Gaucher disease, the inherited deficiency of the enzyme glucocerebrosidase, is the most common
of the lysosomal storage disorders. Type 2 Gaucher disease, the most severe and progressive form,
manifests either prenatally or in the first months of life, followed by death within the first years of
life. The rarity of the many lysosomal storage disorders makes their diagnosis a challenge,
especially in the newborn period when the focus is often on more prevalent illnesses. Thus, a
heightened awareness of the presentation of these rare diseases is necessary to ensure their timely
consideration. This review, designed to serve as a guide to physicians treating newborns and
infants with Gaucher disease, discusses the presenting manifestations of Type 2 Gaucher disease,
the diagnostic work-up, associated genotypes and suggestions for management. We also address
the ethical concerns that may arise with this progressive and lethal disorder, since currently
available treatments may prolong life, but do not impact the neurological manifestations of the
disease.

Keywords

Gaucher disease; acute neuronopathic; infant; lysosomal storage disorder; hydrops fetalis;
congenital ichthyosis; enzyme replacement therapy; palliative care

1. Introduction

Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder (LSD) caused
by a deficiency of the enzyme glucocerebrosidase (GCase). It is the most common of the
more than 50 known LSDs, and is traditionally divided into three distinct types based on the
presence and progression of neurological signs [1]. Type 1, non-neuronopathic GD, presents
with vast clinical heterogeneity, ranging from asymptomatic individuals to patients with
severely enlarged organs and bone involvement [2,3]. Type 3 GD is considered the chronic

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neuronopathic form and is likewise accompanied by a spectrum of manifestations, often with visceral involvement as well as impaired horizontal saccadic eye movements, and some patients may develop myoclonic epilepsy, ataxia, or dementia [2,3]. Type 2 GD, or acute neuronopathic GD, presents with neurological involvement within the first months of life and progresses rapidly, culminating in severe degeneration and death in infancy or early childhood [2,3].

While Type 2 GD is rare, its consideration is crucial for an accurate and timely diagnosis, appropriate management, genetic counseling and family planning [4]. It is encountered in all ethnicities. This work describes the signs and symptoms associated with Type 2 GD, management options, ethical concerns and how to establish the diagnosis. It is meant to serve as a guide for physicians and families of patients as they cope with a fatal diagnosis.

2. Phenotypes Associated with Type 2 GD

Patients with Type 2 GD invariably exhibit clinical signs in the first year of life, although the type and severity of manifestations can vary widely [5,6]. While newborns often appear normal at birth and develop neurological signs with a rapid decline in health within the first year [6], others present prenatally or as neonates. Although the visceral and neurological manifestations are fairly consistent, significant phenotypic heterogeneity is still observed. In the following sections we describe the key features reported.

2.1. Hydrops fetalis

Hydrops fetalis, characterized by an abnormal accumulation of fluid in multiple body areas, has been associated with several LSDs, including Type 2 GD [4]. While multiple disease processes are associated with hydrops, in over 25% of cases the cause is unknown. A portion of these undiagnosed cases may be due to LSDs that go unrecognized, leaving families unprepared regarding the risks for future pregnancies. Among patients with GD, cases involving hydrops tend to be perinatal lethal disorders and the pathophysiology is not well understood [6,7]. Generally, when hydrops is present in Type 2 GD, the fetus dies *in utero,* or is delivered prematurely and dies within several days of birth [7]. In cases of Type 2 GD without hydrops, fetuses generally reach full term [7].

2.2 Skin abnormalities

Newborns with Type 2 GD may present with congenital ichthyosis, an abnormal skin disorder resulting in shiny, almost cellophane-like skin. This is referred to as the collodion-baby phenotype [6,8]. The skin peels over the initial few weeks of life but then typically resolves while other symptoms worsen [6,9]. This pathology is thought to result from altered ratios of ceramides to glucosylceramides in the outermost layers of skin [10]. When severe, the skin must be treated aggressively with lubricants and fluids. Patients must be monitored vigilantly because of the risk for excessive loss of fluid and electrolytes.

2.3. Hepatosplenomegaly

Hepatosplenomegaly, enlargement of both the liver and spleen, is one of the characteristic signs observed among patients with all three types of GD [7]. Often a first diagnostic clue

can be the discovery of an enlarged spleen in the newborn nursery. Untreated, the enlargement can be massive, with organs that extend to the pelvic brim, compromising feeding and breathing. However, some infants may not exhibit prominent organomegaly.

2.4. Thrombocytopenia and anemia

Thrombocytopenia is observed among all forms of GD and occurs in approximately 40% of patients with Type 2 GD [7], either transiently during the neonatal period or as the disease progresses. Anemia is also frequently observed in these patients [6].

2.5. Dysmorphology

Dysmorphic facial features, often associated with other specific LSDs but generally not GD, have been described in some infants with Type 2 GD, including low-set ears and a small, upturned nose with a flat nasal bridge [6,7]. Dysmorphic features often accompany the collodion-baby phenotype and might result from the presence of a thick membranous layer and decreased skin elasticity *in utero*.

2.6. Neurological Involvement

All patients with Type 2 GD experience a rapid neurological decline, but manifestations vary widely. Some patients present with arthrogyphosis (joint contractures), microcephaly (abnormally small head circumference) or hypokinesia (decreased bodily movement) [6,7]. More common neurologic signs include a hyperextended neck, spontaneous apnea, hypertonia, and poor suck and swallow reflexes [6-8]. The characteristic facies and neck extension observed are thought to be secondary to a cervico-facial dystonia. Strabismus is also commonly seen. Many patients go on to develop seizures, rigidity and opisthotonos as the disease progresses.

3. Establishing the Diagnosis of Gaucher Disease

The recommended diagnostic workup for Type 2 GD is outlined in Figure 1. The most reliable diagnostic methods are measurement of glucocerebrosidase enzymatic activity and direct sequencing of *GBA1*. Glucocerebrosidase enzymatic activity is usually included when ordering lysosomal panels, although it is important to assist the laboratory by providing appropriate clinical information. Also, unlike other lysosomal storage disorders, the enzymatic diagnosis of GD cannot be performed on plasma or RBCs, for only nucleated cells can be used. Enzymatic assays can be performed on leukocytes, fibroblasts, amniocytes or tissue samples such as liver or spleen. Type 2 GD is often difficult to distinguish from Types 1 and 3 based solely on enzymatic activity or genotype, although total absence of glucocerebrosidase is associated with early lethality.

Genetic testing for GD by direct sequencing of *GBA1* can be used to determine disease and carrier status [11]. Over 300 mutations in *GBA1* have been identified, and more continue to be discovered. Because there is a nearby pseudogene sharing 96% homology with *GBA1* in the coding regions, genotyping can be challenging as several mutations originate from the pseudogene sequence, and it is essential to differentiate between the two sequences. Further complicating molecular diagnosis, many mutations are rare or private point mutations,

insertions, deletions or splice-site changes that may not be detected in limited mutation screens. Some mutations appear to have arisen as a result of a recombination event that occurred between *GBA1* and its homologous nearby pseudogene and are referred to as recombinant alleles. These alleles are relatively common among infants with Type 2 GD. Since recombinant alleles may result in the introduction of more than one alteration on the same allele, the entire sequence must be carefully analyzed. Generally, the enzyme assay is not reliable for heterozygote detection, and DNA tends to be far more accurate, especially in families where the *GBA1* mutations are known.

Patients with Type 2 GD exhibit epidermal abnormalities regardless of whether ichthyosis is clinically evident [9,12]. 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 differentiate between patients with Type 2 versus Type 3 GD. However, such evaluations are currently performed on a research-only basis [13].

While it is not a recommended method for diagnosis, many affected infants have been identified as a result 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. Among Ashkenazi Jewish families the carrier frequency is about 1 in 16; however neuronopathic forms of GD are relatively uncommon in this population [14].

4. Genotype/Phenotype Correlation

It is generally difficult to predict disease progression in GD based on the *GBA1* genotype. Table 1 summarizes the genotypes and clinical features of 77 patients with Type 2 GD described in the literature. The nomenclature for each amino acid changes encountered in *GBA1* has recently been revised to take into consideration the 39 amino acid leader sequence and thus mutation reports can be a source of some confusion. We have included both designations with the newer versions in parenthesis. 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) [15]. 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 [16]. 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 are 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 [17]. 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.

5. Pathophysiology

It is still not known why only a subset of patients with GD develops aggressive neurodegeneration. Elucidating the etiology has additional relevance because mutations in *GBA1* are a risk factor for developing Parkinson disease [18]. The deficiency of GCase in patients leads to the accumulation of glucosylceramide (GlcCer) and glucosylsphingosine (GlcSph) in many tissues, including the brain. Measurements of GlcCer and GlcSph in brain samples from patients with GD reveal that GlcSph is greatly elevated in neuronopathic GD, with the highest levels seen in Type 2 [19]. Recent work by Futerman and colleagues using a mouse model of neuronopathic GD found that the continued accumulation of GlcCer reaches a critical threshold that triggers a rapid cascade leading to neuroinflammation and neurodegeneration in certain brain regions [20,21].

The role of necroptosis in the pathogenesis of Type 2 GD has also been explored and considered as a potential therapeutic target based on work animal models [22]. Cell death occurs in a regulated manner via necrotic mechanisms, beginning with the formation of the necrosome, a multiprotein complex which includes receptor-interacting protein kinase-1 (RIPK1) and RIPK3 [23]. Necrosome formation can be initiated by ligand binding to death receptors and toll-like receptors, among others [23]. A caspase inhibitor must be present to prevent the complex from following a caspase-dependent apoptotic pathway [23]. Modification of RIPK1 and RIPK3 activate the kinases, beginning a downstream signaling cascade resulting in necroptotic cell death [23]. Active RIPK1 and RIPK3 levels were elevated in brain tissue of Gaucher mice generated by a conditional knock-out strategy. Furthermore, *Ripk3*$^{-/-}$ knock-out mice treated with the highly specific glucocerebrosidase inhibitor, conduritol-beta-epoxide, had fewer neurologic and systemic manifestations and greater longevity compared to similarly treated control mice [22]. These observations support the role of necroptosis in neuronopathic forms of GD, but further studies are needed in human tissues.

6. The Management of Patients with Type 2 Gaucher Disease

Management of Type 2 GD can be challenging for physicians as well as for the patients' families. It is not the intent of this article to present rigid management guidelines, as many cultural, financial and ethical considerations come into play. Common management challenges and suggestions are also outlined in Table 2.

6.1. Failure to thrive and feeding difficulties

Failure to thrive is a common finding in patients with Type 2 GD and results from a combination of anorexia, nausea, hypotonia or hypertonia, vomiting and feeding difficulties [6]. Chewing difficulties, a weak suck, and/or problems with swallowing occur due to neurological involvement. In addition, the presence of abnormal neck tone and opisthotonos, trismus and/or the presence of laryngospasm can be contributing factors [24]. When the diagnosis is reached at an early stage, oral feeding may still be possible. A clinical evaluation of feeding should be performed by a speech pathologist, and infants should be monitored for weight gain, dehydration and/or signs of aspiration [25]. A video fluoroscopic evaluation of swallowing (modified barium scan) provides further information regarding the presence of aspiration, gastro-esophageal reflux and laryngeal penetration with different types of feedings [25] and can be used to adjust the type of bottle/nipple, formula thickening or recommend strict enteral feeding. It can also provide objective evidence for the extent of bulbar involvement [24,26]. The images can be used as an educational tool in discussions regarding the advantages and disadvantages of oral versus gavage feedings. In cases when it is decided to switch to enteral feedings, a nasogastric tube or gastric tube insertion with gastrostomy are two acceptable approaches. Decisions regarding the most appropriate approach should take into account potential anesthesia- related complications during a gastrostomy or gastric tube insertion procedure [27].

Assessment of macronutrient, micronutrient and fluid intake is important in these patients because their oral intake is usually low. An individualized nutrition plan should be constructed, considering the mode of feeding and energy requirements. Patients with Type 2 GD may not gain weight even with enteral or parenteral feeding because of increased resting energy expenditure [28].

6.2. Bulbar involvement and airway compromise

Brain stem degeneration leads to bulbar involvement, characterized by choking events, laryngeal spasm and apnea. These frightening episodes occur in a subset of patients and tend to occur with increased frequency as the disease progresses [29]. Laryngospasm can also lead to hypoxemia, which may accelerate the disease process. Treatment of gastro-esophageal reflux and strict enteral feeding can decrease the incidence of these events in early stages of the disease, but spontaneous episodes may occur as the disease worsens [29]. Excessive oral secretions may also contribute to respiratory symptoms, necessitating suction. Treatment with sublingually delivered ophthalmic atropine drops has been used with some success [30].

Whether to place a tracheotomy tube is one of the most challenging issues faced by physicians and families caring for children with Type 2 GD. A tracheostomy has been effectively used when the primary manifestation is laryngospasm and airway compromise. While in general patients with Type 2 GD who undergo tracheostomy placement tend to survive longer, consideration that this intervention may prolong suffering should be discussed with the family [31]. Extensive dialogue regarding realistic expectations is desirable prior to undertaking this measure. Parents should be counseled that the decision not to undergo tracheotomy can be very reasonable in many circumstances.

There is an increased risk for anesthesia-related complications due to increased secretions, gastro-esophageal reflux, poor control of laryngeal musculature and/or laryngeal spasm. These may be triggered by pre-anesthesia medications or manipulation of the airway [27]. Difficult airway access may require the need for smaller endotracheal tubes [27]. Pulmonary involvement in GD is another risk factor for anesthesia-related complications.

6.3. Neurological aspects

Neurological involvement can manifest as irritability and spasticity. Non-pharmacological treatments include gentle handling, maintaining a calm and familiar surrounding, physical therapy and proper positioning [32]. Pharmacological treatment with benzodiazepines can be useful for both irritability and spasticity. Caregivers should be educated about possible side effects including sedation, constipation, urinary retention, hypersalivation and weakness. Respiratory depression can be seen with benzodiazepine toxicity. Airway compromise due to bulbar involvement may limit their use. Other anti-spasticity drugs used include baclofen, dantrolene and tizanidine [33]. These medications can be offered in the setting of palliative therapy [32].

Seizures, sudden episodes of sensory disturbance, loss of consciousness, or convulsions, associated with abnormal electrical activity in the brain, can occur as the disease progresses. Electroencephalography (EEG) can identify abnormal brain activity in the absence of clinical signs. Findings on EEG may include slowing and disorganization of the background and/or epileptiform activity [Prows:1997bh; 33]. Myoclonic epilepsy and myclonus are often described although not universally, and are thought to be mainly of cortical origin [29,34].

Seizure control can be very challenging in patients with type 2 GD. Careful attention to the identification of treatable etiological factors such as hypoglycemia, hypocalcemia, hyponatremia, hypomagnesemia, hypoxia, intracranial hemorrhage, hyperammonemia, and/or infections is of critical importance. High quality neuroimaging and accurate EEG interpretation may help in optimizing patient care and outcomes [35]. Continuous EEG monitoring for the detection of subclinical seizures is recommended, but may not be possible due to the need for specialized training and access to equipment [36]. Periodic conventional EEG monitoring is more generally available. Antiepileptic treatment is generally guided by the particular epilepsy syndrome at presentation [37]. However, benzodiazepines are usually first-line therapy for status epilepticus although they can cause respiratory depression and/or cardiac dysrhythmia. Midazolam and lorazepam are the preferred agents. Second-line therapies include phenytoin and fosphenytoin. Phenytoin has been associated with local skin necrosis and hypotension. Both agents can cause cardiac dysrhythmias with more rapid administration. Phenobarbital is frequently used in infants, but carries the risk of hypotension, respiratory depression, and cardiac arrhythmia. Levetiracetam can also be considered. Valproate can be effective but patients must be monitored for potential side effects such as thrombocytopenia and hepatotoxicity [38].

6.4. Visceral and hematologic involvement

Visceral involvement presents as splenomegaly and is associated with anemia and thrombocytopenia. Liver enlargement is also seen, and can be accompanied by elevations in transaminases. Portal hypertension and liver dysfunction are rarely described in Type 2 GD, although neonatal cholestasis is occasionally seen and may precede other manifestations [39,40]. Splenectomies have been performed in these patients but are generally not recommended due to the risk of surgical complications. It is important to note that the absence of overt organomegaly is not sufficient to rule out the diagnosis of Type 2 GD.

The main hematological complication is a bleeding tendency secondary to the thrombocytopenia and abnormal platelet aggregation [41]. A decrease in clotting factors secondary to consumption by an enlarged spleen has also been described [42]. The complete blood cell count should be monitored regularly to identify the need for transfusions. Systemic disease can be minor or almost absent in comparison to the neurological deficits observed in patients with Type 2 GD.

Pulmonary involvement with interstitial lung disease is a common finding primarily resulting from recurrent aspirations [6] or from the infiltration of alveolar, interstitial, perivascular, and peribronchial spaces by lipid-laden macrophages [43]. Chest X-ray may show diffuse interstitial infiltration in both lung fields, and a ground glass pattern can be seen on chest CT. On lung biopsy, Gaucher cells can be seen [43]. Periodic monitoring of pulmonary involvement should include examination for evidence of respiratory distress, oxygen saturation measurements, and chest X-rays. Such testing can identify the need for supportive treatment with oxygen and/or antibiotics if there is evidence for aspiration pneumonia. Fever may be a sign of a pulmonary infection, but can also be present in the absence of infection due to inflammation, possibly mediated by activated glucosylceramide-laden macrophages [6]. Prolonged, unexplained fever has been associated with a worsening disease course [29].

7. Treatment

7.1. Enzyme replacement and substrate reduction

Enzyme replacement therapy (ERT) can ameliorate the visceromegaly and hematologic abnormalities in patients with Type 2 GD [28,44]. It is not clear whether ERT impacts pulmonary involvement, although when the primary cause of pulmonary involvement is recurrent aspirations secondary to neurological deterioration, ERT is not beneficial [28,44]. The recombinant enzyme does not cross the blood-brain barrier and there is no evidence that ERT has reversed, stabilized, or slowed the progression of neurological involvement [45]. Siblings were described where one received ERT after diagnosis at 7 months, and the subsequent sibling was treated from birth. While the sibling treated pre-symptomatically survived 6 months longer, the final outcome was the same [45]. It has been debated whether it is ethical to treat Type 2 GD patients with ERT because it is a very costly and inconvenient therapy that may only prolong suffering [46]. It is generally accepted that ERT should be discussed with families presenting both its potential merits and the limitations. Some physicians feel that ERT is not indicated for patients with Type 2 GD, although in

recent years many infants have been started on the therapy [45]. It is sometimes deemed appropriate to treat with ERT until it is clear that the patient does not have Type 3 GD. In addition, it is reasonable to consider therapy for Type 2 GD patients in situations where it could be palliative, for example if reduction of organomegaly would alleviate pain, avoid surgery or facilitate other necessary interventions such as gastric tube placement.

Alternative methods of enzyme delivery have been investigated to treat the neurological deterioration in GD. Intraventricular delivery via a reservoir was attempted without success [47]. An animal study evaluated convection-enhanced delivery (CED) to restore GCase levels in the brains of rats and primates [48]. Enzymatic assays showed significant increases in GCase activity in the white matter, cortex, and pons of treated animals, and immunohistochemical staining confirmed GCase localization in neurons of the cortex [48]. One patient with Type 2 GD was treated with GCase via CED, and while successful delivery of enzyme was documented, there was continued disease progression [49]. Intravascular delivery after disruption of the blood-brain barrier has been investigated but not attempted in these patients [50].

Substrate reduction therapy with Miglustat, an inhibitor of glucosylceramide synthase, was not shown to be beneficial for neurological manifestations in Type 3 GD [51]. This treatment is not indicated for Type 2 GD.

7.2. Bone marrow and hematopoietic stem cell transplantation

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]. Ringden *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 at follow-up ten years later [54]. However, both developed epilepsy 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.

8. Genetic Counseling

Genetic counseling is an important aspect of the care for these patients and families. 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 [56,57]. Thus the recurrence risk is not always obvious.

9. Potential Future Therapies

9.1. Substrate reduction therapy

Inhibitors of glucosylceramide synthase have been explored as a means to attenuate glucosylceramide production and accumulation in various organs. The currently available therapy is not beneficial in neuropathic GD (Type 2 and 3) [51]. A novel glucosylceramide synthase inhibitor decreased substrate accumulation in the brains of a mouse model for neuronopathic GD [58]. 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 [59].

9.2. 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 [60], [[61]. Currently, there is an effort to identify candidate molecules [62,63]. 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 [64]. This GD phenotype in macrophages was successfully reversed with a new molecular chaperone [65].

9.3. Gene therapy

Gene therapy is a potentially promising future therapeutic strategy for genetic diseases with enzymatic deficiencies like GD [66], 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 [66].

9.4. 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 [22] may provide new leads for future drug development.

10. 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. In the midst of 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 [67]. Studies have shown that parents of critically ill children need sensitivity, empathy, follow-up contact and information about counseling from healthcare providers [68]. 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.

Type 2 GD is a progressive condition with an aggressive neurodegenerative course and is therefore particularly appropriate for palliative care. This can be a supportive resource for the parents as well as the child. When it is evident that supportive measures are the only options appropriate for continued care, health care providers can help the parents reengage with a new set of goals. The new goals can include managing the child's condition with the least amount of treatment-related pain or suffering, limiting exposure to invasive or extreme interventions, and maintaining the child's quality of life [67]. This approach might seem very reasonable for some parents and not to others, who choose to continue intensive interventions. Cultural and religious beliefs affect the parental decisions on palliative and end of life care and must be considered [68]. It is important to provide the parents with ongoing counseling by healthcare professionals during the different stages of the disease as well as after the child's death [69].

When possible, the subject of an autopsy should be raised with families. Such postmortem evaluations can help clinicians and researchers to better understand disease pathogenesis. Frozen stored tissue specimens are very useful for many studies that could ultimately impact the care of future children afflicted with this disorder.

Caring for a dying child can have a great impact on both parents and siblings. Appropriate support and therapy should be recommended as needed. Also, with the parents' consent, education of employers, extended family members, and clergy as to the gravity of the illness can help the family get the needed support and time with the child. Engaging the services of hospice can also be very helpful.

11. Conclusion

Diagnosing and treating infants with Type 2 Gaucher disease represents a challenging paradigm for neonatal and genetic illnesses. An accurate and timely diagnosis of GD is critical for genetic counseling, patient management and family planning that can inform future pregnancies. However, the phenotypic heterogeneity observed in Type 2 GD patients makes the diagnosis a challenge for physicians unfamiliar with the disease. In general, Type 2 GD should be considered in the differential diagnosis of infants presenting with splenomegaly, failure to thrive, congenital ichthyosis, hydrops fetalis and in families with recurrent fetal losses. Reliable methods of diagnosing GD include measurement of glucocerebrosidase enzymatic activity and direct sequencing of *GBA1*. Confirmation of the diagnosis of Type 2GD will direct treatment considerations and allow physicians to focus on critical clinical issues. Treating these infants is a challenge, and it is important to involve the medical team, family, and support networks early on, in order to identify goals of treatment and help to cope with this grave diagnosis.

Acknowledgements

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Highlights

Type 2 Gaucher disease is a rare neurodegenerative lysosomal disorder of infancy.

Diagnosis is made by measurement of enzymatic activity and direct sequencing of *GBA1*.

Patients with Type 2 Gaucher disease have multiple different genotypes.

Currently, there is no effective therapy except supportive and palliative treatments.

Management of patients is complex and requires a multidisciplinary approach.
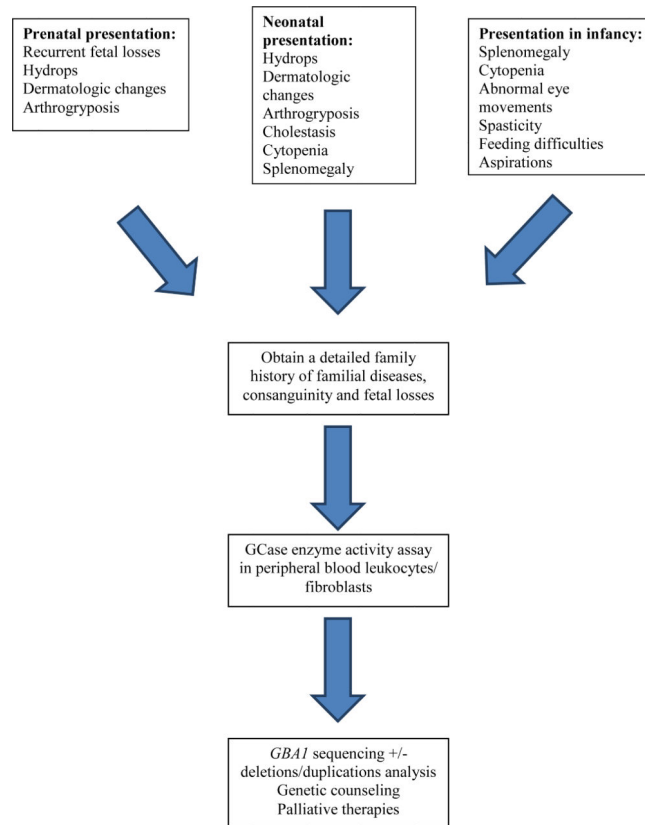
Figure 1.
Establishing the diagnosis of Gaucher disease

Figure 2.
Two patients with Type 2 Gaucher disease demonstrating the characteristic facies and strabismus. Top panel shows the first infant at age 6 months (left) and post-tracheotomy at 16 months (right). Lower panel shows the second child at age 8 months (left) and after tracheotomy at age 2 years.

Figure 3.
Neonatal presentations of Gaucher disease demonstrating organomegaly (top left), hydrops (bottom) and peeling skin (top).

Table 1

Genotypes and significant clinical features observed in patients with Type 2 Gaucher disease

Alleles	Protein	cDNA	Age at diagnosis	Age at death	Hydrops	Ichthyosis	Hepatosplenomegaly	Seizures	Additional clinical information	Reference
55 bp del/Met416Val	p.Met455Val	c.1263del55/c.1363A>G	8 months	17 months				Yes		[12]
55bp del / Arg285His	p.Arg324His	c.1263del55/c.971G>A	At birth	Perinatal					Unknown	[13]
55bp del/Arg257Gln	p.Arg296Gln	c.1263del55/c.887G>A	At birth	3 weeks		Yes	Yes			[13]
Ala190Glu/Gly325Arg	p.Ala229Glu p.Gly364Arg	c.686C>A/c.1090G>A	9 months	Unknown					Unknown	[13]
Arg120Trp/Ser196Pro	p.Arg159Trp p.Ser235Pro	c.475C>T/c.703T>C	At birth	3 months		Yes	Yes	Yes	Laryngospasm	[70]
Arg120Trp/Ser196Pro	p.Arg159Trp p.Ser235Pro	c.475C>T/c.703T>C	At birth	11 days		Yes	Yes	Yes (refractory)		[13]
Arg131Leu/Arg131Leu	p.Arg170Leu p.Arg170Leu	c.509G>T/c.509G>T	5 months	7 months		Yes			Developmental regression	[13]
Arg131Leu/Arg131Leu	p.Arg170Leu p.Arg170Leu	c.509G>T/c.509G>T	Prenatal	9 months		Yes	Yes			[71]
Arg359X/Val398Phe	p.Arg398X p.Val437Phe	c.1192C>T/c.1309G>T	At birth	4 weeks		Yes			Facial dysmorphy (triangular face, malformed ears)	[72]
Arg463His/Arg463His	Arg502His Arg502His	c.1505G>A/c.1505G>A	At birth	1 month		Yes	Yes	Yes (myoclonic)	Respiratory failure	[73]
Asp409His + His255Gln/Asp409His + His255Gln	Arg448His + His294Gln/Asp448His + His294Gln	c.[1342G>C; c.882T>G]/c.[1342G>C; c.882T>G]	1 month	Unknown					Unknown	[74]
Asp409His + His255Gln/Asp409His + His255Gln	Asp448His + His294Gln/Asp448His + His294Gln	c.[1342G>C; c.882T>G]/c.[1342G>C; c.882T>G]	8 months	2 years					Brainstem involvement; developmental regression	[74]
c.533delC/c.533delC		c.533delC/c.533delC	Prenatal	22 weeks gestation	Yes		Yes		External abnormalities (rocker bottom feet, flat nose)	[5,75]
c.84GG/Asp409His	Asp448His	c.84dupG/c.1342G>C	5 months	Unknown					Abnormal eye saccades; delayed cognition	[74]
Cys16Ser/Cys16Ser	Cys55Ser/Cys55Ser	c.164G>C c.164G>C	Postmortem	At birth					Unknown	[76]
Cys16Ser/Cys16Ser	Cys55Ser/Cys55Ser	c.164G>C c.164G>C	Prenatal	33 weeks gestation					4th unsuccessful pregnancy for couple	[76]
Gly202Arg/Gly202Arg	Gly241Arg/Gly241Arg	c.721G>A c.721G>A	5 months	Unknown					Unknown	[13]
Gly202Arg/Gly202Arg	Gly241Arg/Gly241Arg	c.721G>A c.721G>A	6 months	Unknown					Unknown	[13]
His311Arg/His311Arg	His350Arg/His350Arg	c.1049A>G c.1049A>G	Prenatal	At birth	Yes		Yes			[72]
His311Arg/His311Arg	His350Arg/His350Arg	c.1049A>G c.1049A>G	Prenatal	At birth	Yes		Yes			[72]
IVS2 + 1 G>A/Phe251Leu	Phe290Leu	c.115+1G>A/c.870C>A	16 days	1 month					Decreased spontaneous movement	[74]

Alleles	Protein	cDNA	Age at diagnosis	Age at death	Hydrops	Ichthyosis	Hepatosplenomegaly	Seizures	Additional clinical information	Reference
IVS2 + 1 G>A/Phe251Leu	Phe290Leu	c.115+1G>A/c.870C>A	At birth	1 month		Yes	Yes	Myoclonic jerks/tremors		[77]
IVS2 + 1 G>A/RecNciI		c.115+1G>A/*	Prenatal	45 days	Yes	Yes	Yes			[78]
IVS2 + 1 G>A/RecNciI		c.115+1G>A/*	Unknown	Unknown					Oculomotor apraxia; developmental regression	[74]
Leu444Pro + Glu326Lys/Pro182Leu	Leu483Pro + Glu365Lys/Pro221Leu	c.[1448T>C; c.1093G>A]/c.662C>T	At birth	25 days	Yes		Yes			[79]
Leu444Pro/Arg131Cys	Leu483Pro/Arg179Cys	c.1448T>C/c.508C>T	8 months	10.5 months			Yes		Strabismus	[80]
Leu444Pro/Arg257Gln	Leu483Pro/Arg296Gln	c.1448T>C/c.887G>A	Unknown	Unknown					Extensor posturing of trunk and neck; dysconjugate and crossed gaze	[74]
Leu444Pro/Arg257Gln	Leu483Pro/Arg296Gln	c.1448T>C/c.887G>A	9 months	3 years				Yes (myoclonic)		[81]
Leu444Pro/Arg257Gln	Leu483Pro/Arg296Gln	c.1448T>C/c.887G>A	7 months	Unknown			Yes		Strabismus; bilateral hearing loss; failure to thrive	[77]
Leu444Pro/Asp380Asn	Leu483Pro/Asp419Asn	c.1448T>C/c.1255G>A	Unknown	Unknown					Unknown	[74]
Leu444Pro/c.330delA	Leu483Pro	c.1448T>C/c.330delA	3 months	Unknown					Unknown	[13]
Leu444Pro/Gln414X	Leu483Pro/Gln453X	c.1448T>C/c.1357C>T	9 months	10 months					Apneic spells; developmental regression; ophthalmoplegia	[74]
Leu444Pro/Gln414X	Leu483Pro/Gln453X	c.1448T>C/c.1357C>T	2 months	10 months					Unknown	[74]
Leu444Pro/Gly202Arg	Leu483Pro/Gly241Arg	c.1448T>C/c.721G>A	8 months	2.5 years				Yes (tonic)		[81]
Leu444Pro/Ile260Thr	Leu483Pro/Ile299Thr	c.1448T>C/c.896T>C	6 months	21 months					Strabismus; facial dysmorphy; respiratory difficulties	[79]
Leu444Pro/IVS2 + 1 G>T	Leu483Pro	c.1448T>C/c.115+1G>T	6 months	9 months					Brainstem involvement; developmental regression	[74]
Leu444Pro/IVS 2+1G>A	Leu483Pro	c.1448T>C/c.115+1G>A	4 months	Unknown					Unknown	[13]
Leu444Pro/IVS 2+1G>A	Leu483Pro	c.1448T>C/c.115+1G>A	4 months	Unknown					Unknown	[13]
Leu444Pro/IVS2 + 1G>A	Leu483Pro	c.1448T>C/c.115+1G>A	6.5 months	1 year					Strabismus; hypotonia; swallowing difficulties	[82]
Leu444Pro/IVS2 + 1G>A	Leu483Pro	c.1448T>C/c.115+1G>A	At birth	9 months			Yes		Progressive difficulty swallowing; bilateral brain stem dysfunction	[82]
Leu444Pro/IVS2 + 1 G>T	Leu483Pro	c.1448T>C/c.115+1G>T	Unknown	8.5 months					Apnea; hypotonia; hyperflexia; esotropia	[74]
Leu444Pro/Leu385Pro	Leu483Pro/Leu424Pro	c.1448T>C/c.1271T>C	11 months	18 months				Yes	Ophthalmoplegia	[12]
Leu444Pro/Leu444Pro + Ala456Pro	Leu483Pro/Leu483Pro + Ala495Pro	c.[1448T>C; [1448T>C; c.1453G>C]	7 months	10 months			Yes		Strabismus	[82]
Leu444Pro/Phe213Ile	Leu483Pro/Phe252Ile	c.1448T>C/c.754T>A	1 year	28 months					Ophthalmoplegia	[12]
Leu444Pro/Phe213Ile	Leu483Pro/Phe252Ile	c.1448T>C/c.754T>A	11 months	Unknown					Bone involvement; ophthalmoplegia	[12]
Leu444Pro/RecNciI	Leu483Pro	c.1448T>C/*	5 months	1 year			Yes		Strabismus; facial paralysis; poor gag	[8]
Leu444Pro/RecNciI	Leu483Pro	c.1448T>C/*	1 year	22 months					Abnormal tone	[12]
Leu444Pro/RecNciI	Leu483Pro	c.1448T>C/*	8 months	18 months				Yes	Ophthalmoplegia	[12]

Alleles	Protein	cDNA	Age at diagnosis	Age at death	Hydrops	Ichthyosis	Hepatosplenomegaly	Seizures	Additional clinical information	Reference
Leu444Pro/RecNcil	Leu483Pro	c.1448T>C*	1 month	6 months					Unknown	[74]
Leu444Pro/Thr323Ile	Leu483Pro/Thr362Ile	c.1448T>C/c.1085C>T	6 months	Unknown				Hand tremors	Strabismus; brainstem involvement; clonus in feet	[74]
Leu444Pro/Tyr304Cys	Leu483Pro/Tyr343Cys	c.1448T>C/c.1028A>G	1 year	Unknown					Unknown	[13]
Leu444Pro/Tyr304Cys	Leu483Pro/Tyr343Cys	c.1448T>C/c.1028A>G	1 year	2 years				Yes (myoclonic)		[81]
Leu444Pro/Tyr304Cys	Leu483Pro/Tyr343Cys	c.1448T>C/c.1028A>G	1 year	Unknown					Unknown	[74]
Leu444Pro/Tyr313His	Leu483Pro/Tyr352His	c.1448T>C/c.1054T>C	7 months	10 months					Oculomotor apraxia; developmental regression	[74]
Leu444Pro/Unknown	Leu483Pro	c.1448T>C	7 months	11 months			Yes	Yes	Strabismus	[8]
Leu444Pro/Unknown	Leu483Pro	c.1448T>C	Unknown	Unknown					Unknown	[74]
Leu444Pro/Unknown	Leu483Pro	c.1448T>C	8 months	2.5 years			Yes	Yes	Absent gag	[8]
Lys198Glu/Lys198Glu	Lys237Glu/Lys237Glu	c.709A>G/c.709A>G	16 months	2 years			Yes	Yes (myoclonic)		[81]
Lys198Glu/Lys198Glu	Lys237Glu/Lys237Glu	c.709A>G/c.709A>G	Unknown	Unknown				Myoclonic jerks	Hypotonia; gaze abnormalities	[74]
Phe213Ile/Asn382Lys	Phe252Ile/Asn421Lys	c.754T>A/c.1263C>A	10 months	18 months					Unknown	[12]
Phe213Ile/Leu383Arg	Phe252Ile/Leu422Arg	c.754T>A/c.1265T>G	7 months	26 months				Yes		[12]
Phe213Ile/Lys74X	Phe252Ile/Lys113X	c.754T>A/c.337A>T	Unknown	10 months				Yes (myoclonic)	Strabismus; ophthalmoplegia; apneic spells	[74]
Phe259Leu/Asn188Lys	Phe298Leu/Asn227Lys	c.894C>A/c.681T>G	At birth	Perinatal					Opisthotonus	[13]
Pro122Leu/Val375Leu	Pro161Leu/Val414Leu	c.482C>T/c.1240G>C	1 year	Unknown				Yes		[12]
RecA/IVS 10 + 2		* c.1505+2T>G	Prenatal	Prenatal	Yes	Yes			Ascites; pleural effusions	[74]
RecA/IVS 10+2 T>G		c.1505+2T>G	Prenatal	Prenatal termination	Yes					[82]
RecB/RecB		*	Prenatal	1 day	Yes	Yes	Yes		Facial dysmorphy	[8]
RecB/RecB		*	Prenatal	Miscarriage	Yes				Thymic hypoplasia	[8]
RecD/RecD		*	Prenatal	Perinatal	Yes	Yes				[13]
RecD/RecD		*	Prenatal	2 hours	Yes	Yes	Yes			[83]
RecD/RecD		*	Prenatal	1 hour	Yes	Yes	Yes		Hypokinesia; facial dysmorphy	[84]
RecG + Leu444Pro/Arg257Gln	Leu483Pro/Arg296Gln	* c.1448T>C/c.887G>A	6 months	Unknown					Unknown	[13]
RecNcil/Glu41Leu	Glu80Leu	* c.238G>A	Several months	18 months			Yes		Failure to thrive	[80]
RecNcil/RecNcil		*	Prenatal	At birth	Yes		Yes		Hyperextension of neck	[71]
Ser196Pro/Ser196Pro	Ser235Pro/Ser235Pro	c.703T>C c.703T>C	At birth	Perinatal					Respiratory difficulty	[13]

Alleles	Protein	cDNA	Age at diagnosis	Age at death	Hydrops	Ichthyosis	Hepatosplenomegaly	Seizures	Additional clinical information	Reference
Trp184Arg/Asp409His	Trp223Arg/Asp448His	c.667T>C c.1342G>C	5 months	Unknown					Opisthotonos; hypertonia; increased gag reflex	[74]
Tyr363Cys/Unknown	Tyr402Cys	c.1205A>G	5 months	15 months				Yes		[12]
Unknown/Unknown			At birth	2 months			Yes		Hyperextension of the neck; hypertonia; poor suck/swallow	[85]
Unknown/Unknown			At birth	1 week		Yes			Flat nose	[85]

*
Rec D: recombination at the end of exon 7; Rec G: recombination in intron 10-exon 11 or the 3' untranslated region; Rec A: Recombination in intron 10-exon 11 or the 3' untranslated region; Rec A: Recombination in intron 3; Rec N*cil*: Recombinant allele in exon 10 containing L444P, A456P, and V460V

Table 2

Managing common clinical features of Type 2 GD

Clinical feature	Recommended evaluation	Management
Feeding difficulties and failure to thrive	Exam by a speech pathologist Video fluoroscopy to assess swallowing and aspirations Nutrition assessment	Modification of bottle type / formula thickening Consider strict enteral feeding per nasogastric tube / gastric tube Individualized nutrition plan with sufficient macro and micronutrients
Gastrointestinal reflux	Clinical diagnosis Can be demonstrated on video fluoroscopy and pH meter	Head elevation Proton pump inhibitors / H2 blockers
Laryngeal spasm/choking/apnea	Consider ENT evaluation	Treat GE reflux Atropine drops for excess salivation Consider strict enteral feeding Consider tracheostomy although may prolong survival Take precautions when performing anesthesia
Spasticity / abnormal movements	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