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Diagnosing neuronopathic Gaucher disease: New considerations and challenges in assigning Gaucher phenotypes

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Abstract

Gaucher disease (GD), resulting from biallelic mutations in the gene *GBA1,* is a monogenic recessively inherited Mendelian disorder with a wide range of phenotypic presentations. The more severe forms of the disease, acute neuronopathic GD (GD2) and chronic neuronopathic GD (GD3), also have a continuum of disease severity with an overlap in manifestations and limited genotype-phenotype correlation. In very young patients, assigning a definitive diagnosis can sometimes be challenging. Several recent studies highlight specific features of neuronopathic GD that may provide diagnostic clues. Distinguishing between the different GD types has important therapeutic implications. Currently there are limited treatment options specifically for neuronopathic GD due to the difficulty in delivering therapies across the blood-brain barrier. In this work, we present both classic and newly appreciated aspects of the Gaucher phenotype that can aid in discriminating between acute and chronic neuronopathic GD, and highlight the continuing therapeutic challenges.

Keywords

Gaucher disease; neuronopathic; *GBA1*; glucocerebrosidase; newborn screening; next-generation sequencing

1.0 Introduction

Pathogenic biallelic variants in the gene *GBA1* disrupt the function of the lysosomal glycoside hydrolase glucocerebrosidase (GCase, EC 3.2.1.45) and result in the lysosomal

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Website Reference

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storage disorder (LSD) Gaucher disease (GD). GD is divided into three types based on the presence and progression of neurological manifestations: non-neuronopathic (GD1, OMIM 230800), acute neuronopathic (GD2, OMIM 230900), and chronic neuronopathic (GD3, OMIM 231000). Each type displays broad phenotypic and genotypic heterogeneity [1, 2]. GD2, the most severe form of the disease, while uniformly devastating, presents in different ways, including with prominent visceral involvement, hydrops fetalis, congenital ichthyosis, thrombocytopenia, failure to thrive, strabismus and dysphagia. Patients with GD2 typically die in infancy or early childhood, although interventions including enzyme replacement therapy (ERT), bone marrow transplant, tube feedings, and tracheostomy can prolong life [3]. The clinical heterogeneity seen in GD3 has resulted in further subclassifications. Type 3b, the most common subtype, is characterized by impaired saccadic eye movements in addition to extensive visceral involvement. The other two currently defined subtypes, type 3a, distinguished by development of myoclonic epilepsy, and type 3c, which uniquely involves aortic calcification, hydrocephalus and/or corneal opacities, are less common [4].

While genotype-phenotype correlations in GD are often limited, there are a few specific instances where the patient's genotype can aid in identifying neuronopathic GD (nGD). Homozygosity or compound heterozygosity for mutation p.N409S (N370S) is not seen with nGD. Another common genotype, p.L483P/p.L483P (L444P/L444P), is most frequently associated with GD3 [5, 6]. However, homozygosity for a null allele, or a null allele in conjunction with a p.L483P allele, is more likely to be associated with GD2. Nevertheless, with more than 500 mutations associated with GD, it is frequently difficult to predict phenotype or prognosis from the genotype. New technologies and policies, such as next generation sequencing (NGS) and newborn screening (NBS), are resulting in an earlier diagnosis of GD. This has increased the urgency for criteria to distinguish between the different GD types since the prognosis is so critically different. Clinical diagnosis via enzyme activity assays and genotyping reliably establish an initial diagnosis of GD; however, ongoing clinical assessments are often necessary to determine the specific GD type. Discerning the appropriate type remains important in order to implement appropriate treatment and care, which varies dramatically between GD2 and GD3. This review aims to delineate several newer features relevant in diagnosing and treating nGD, while describing remaining challenges.

2.0 Diagnosing Gaucher disease and its types

2.1 Pre-clinical diagnosis

A pre-clinical diagnosis of GD can be achieved through NBS, prenatal testing, family testing, and carrier screening. Since the early 2000s, pilot studies of NBS for GD have been performed in the United States, and five states now test for GD as part of their standard NBS [7, 8]. However, GD is not on the federal list of recommended diseases that states are encouraged to include in their NBS panel (hrsa.gov). In contrast to the broad applications of NBS, neither prenatal screening nor carrier screening for GD are widely preformed except in at-risk populations, such in the Ashkenazi Jewish population [9]. Even within at-risk populations, because of the high incidence of milder GD, prenatal and carrier screening are controversial. Prenatal screening typically consists of measuring GCase activity in amniotic

fluid or chorionic villi samples [10, 11]. Others have proposed measuring the levels of a biomarker for macrophage activity that is significantly elevated in patients with GD, plasma chitotriosidase, in the amniotic fluid [12, 13]. Additional studies have demonstrated the feasibility of measuring glucosylsphingosine (lyso-Gb1), a metabolite of glucosylceramide (Gb1) which accumulates due to GCase dysfunction, in dried blood spots of neonates [14, 15]. Lyso-Gb1 has been found to be elevated in patients with GD compared to healthy controls, and is generally higher in nGD than in GD1 [16]. Carrier screening is a less invasive option than prenatal testing as it entails evaluating the *GBA1* sequence or screening for specific common mutations in both parents and assessing the potential risk of having a child with GD. However, carrier screening, especially when based on a limited panel of mutations, may miss rarer pathological variants, providing false reassurance [17].

Given the vast clinical heterogeneity as well as the limited genotype-phenotype correlation, diagnosing GD pre-clinically may pose an ethical dilemma. Current NBS criteria purposefully excludes late-onset disorders due to unclear patient consent and questionable benefits of a diagnosis made in the early years of life [18]. On the other hand, an early diagnosis of GD can minimize the emotional and financial burden that families may experience resulting from a prolonged diagnostic odyssey. Furthermore, starting patients with visceral manifestations on ERT early can help to ameliorate or prevent disease involvement as bone crises, organomegaly and anemia [5, 19, 20], although some patients with nGD on ERT continue to have visceral and skeletal complications. Since there currently is no effective treatment for the neuronopathic features of GD, there is no clear benefit of an early nGD diagnosis with regard to the treatment or prevention of neurological manifestations [21, 22]. Furthermore, there are few effective treatment options for patients with GD2; however, an early diagnosis can provide families with more time to process their child's prognosis and to arrange palliative care or fully explore therapeutic options prior to further disease progression. Importantly, infrastructure such as genetic counselors and physicians with experience treating GD is essential for continual support of newborns diagnosed with GD and their families [23]. All patients diagnosed pre-clinically should receive regular evaluations to monitor disease progression and to initiate appropriate interventions.

2.2 Diagnosing Gaucher disease after the onset of disease manifestations

Beginning in the mid-20th century, the diagnosis of GD was most commonly achieved by assessing the patient's clinical findings, with confirmation provided by an enzyme activity assay measuring GCase levels or by the identification of Gaucher cells in bone marrow biopsies or removed spleens. Today, biopsies are not needed in order to establish the diagnosis, and are indicated only rarely to exclude other diseases or complications. Established methods of assessing GD manifestations include ultrasounds, x-rays, MRIs, blood tests, and neuro-ophthalmologic evaluations. Certain phenotypes are viewed as typical to a specific subtype, such as myoclonic epilepsy to GD3a and hydrops fetalis and ichthyosis to GD2; yet only some patients display these defining phenotypes.

With advances in genetic sequencing, a molecular diagnosis of GD has become another common means of validating an initial clinical diagnosis of GD, as well as a first-line

method for diagnosing patients. Novel pathogenic *GBA1* variants continue to be discovered, as well as unique genotypes due to atypical mutation mechanisms, and this constantly evolving genetic information continues to muddle genotype-phenotype correlations within the different GD types [24].

2.3 Diagnoses based on Next Generation Sequencing

In the past decade, the advent, increased availability, and decreased cost of NGS has become instrumental in its more widespread use in establishing challenging diagnoses. Increasingly, young children with failure to thrive, developmental delay or neurodegeneration are being referred to Undiagnosed Disease Clinics or to specialists who are ordering whole genome sequencing or whole exome sequencing to provide diagnosis [25, 26]. The resulting identification of established pathological variants has led to an early diagnosis of nGD in many cases. However, when novel *GBA1* variants are found, these results can be challenging to interpret. In addition, recombinant alleles resulting from genomic recombination with the highly homologous *GBA1* pseudogene [27] can be difficult to detect by this method. Such recombinant alleles are especially prevalent in GD2 [28].

2.4 Atypical mutational mechanisms

Despite its classification as an autosomal recessive Mendelian disorder, rarely, other mutational mechanisms have been encountered in patients with GD which can introduce some confusion. A 2008 case report described a patient with both GD3 and Charcot-Marie-Tooth disease type I (CMT1) as a result of uniparental disomy [29]. Additional atypical mechanisms of disease found in patients with GD include somatic mosaicism and single *GBA1* alleles with two variants in *cis* [30, 31]. Such complex modes of inheritance can pose challenges in genotyping, and at least one case study demonstrated the misdiagnosis of GD1 in a woman receiving carrier testing who had two variants on one of her *GBA1* alleles [32]. Ensuring that both copies of the proband's *GBA1* are sequenced and evaluating parental DNA can aid in genotyping accuracy. These atypical cases have important implications for genetic counseling, and precise genotyping of each family member can help counselors provide more accurate risk assessments and improved prenatal counseling [30].

Similar to other disease-implicated genes, the number of pathogenic variants that have been identified in *GBA1* has increased with more widespread sequencing. One 2018 study of 20 Chinese patients with GD2 led to the characterization of six novel variants [6]. Other studies in the past few years assessing genotypes of patients in Spain, the Philippines, and Turkey have revealed additional novel variants [33–35]. Genetic counselors and other healthcare professionals working with patients with GD should remain abreast of the most current literature detailing pathogenic variants.

3.0 Diagnosing type 2 Gaucher disease

Because patients with GD2 can present prenatally, in the newborn period, or later during the first year of life, it is important for obstetricians, neonatologists and general pediatricians to consider GD in the differential diagnosis of patients with suggestive symptomatology.

3.1 Neuronopathic Gaucher disease presenting in the newborn

Gaucher disease should be considered when neonates present with hydrops fetalis or ichthyosis. Other disease phenotypes, including extreme hepatosplenomegaly and congenital thrombocytopenia can bolster a diagnosis of GD.

3.1.1 Hydrops fetalis—On the most severe end of the neurological manifestation spectrum is hydrops fetalis, which is characterized by abnormal accumulation of fluid in different body parts [28, 36]. Identification of hydrops fetalis as an early manifestation of several LSDs has led to an appreciation that 15–29% of unexplained nonimmune hydrops fetalis cases are caused by LSDs [37, 38]. It is now clear that a perinatal lethal form of GD2 should be considered when hydrops fetalis is detected prenatally. Hydrops fetalis can also lead to death *in utero*, and it is not uncommon for couples to lose several pregnancies prior to becoming aware of a diagnosis of an LSD [39, 40]. Recognizing the prevalence of LSDs resulting in hydrops, one group recently developed a hydrops fetalis NGS panel that utilizes amniotic fluid that could potentially aid in the rapid diagnosis of LSDs [41]. Furthermore, there are important implications for the genetic counseling of parents of patients with hydrops fetalis [40, 42].

3.1.2 Congenital ichthyosis—Another GD2 phenotype was first appreciated after studying a null allele GD2 mouse model, which displayed ichthyotic skin, dehydration and perinatal death [37, 43]. Babies with this phenotype present at birth with dry peeling skin and several infants have been described as “collodion babies”, infants born with a cellophane-like membrane covering their skin. Since the recognition that GD falls into the differential diagnosis of congenital ichthyosis, further cases have come to medical attention with increased frequency [44].

3.1.3 Other manifestations in perinatal lethal Gaucher disease—Case reports of perinatal lethal GD also describe other severe manifestations including hepatosplenomegaly, biliary atresia, facial dysmorphology, arthrogryposis congenital thrombocytopenia (or the blueberry muffin phenotype) and growth retardation [45, 46]. Perinatal autopsies and collection of fluids such as bronchoalveolar lavage fluid, chorionic villi, and amniotic fluid are important for confirmation by sequencing *GBA1*, detecting Gaucher cells or assessing GCase activity [45, 47–49].

3.2. Diagnosing GD2 in young infants

Most infants with nGD reach medical attention due to failure to thrive, choking, stridor, seizures, unusual eye movements, or developmental delay. Since most of these findings are non-specific, there is often a prolonged diagnostic odyssey. The finding of features such as hepatosplenomegaly, anemia or thrombocytopenia can increase the index of suspicion, although these features are common to all three types of GD and may appear after the onset of neurological involvement. However, two specific studies, the swallow evaluation and examination of skin ultrastructure, can be useful in establishing the diagnosis of GD2.

3.2.1 Evaluating swallow—A noticeable decline in the ability to swallow is a common feature in patients with GD2, and the gold standard for assessing dysphagia is the modified

barium swallow (MBS) [50]. Interpreting results of the MBS, however, often becomes subjective, which affects diagnostic accuracy and prevents further insights into disease stage [51, 52].

Seehra et al. recently analyzed dysphagia in 11 patients with GD2 and used principal component analysis (PCA) and transition analysis to identify five parameters that effectively encompass specific aspects of swallowing. After evaluating MBS results with these five parameters, patients with GD2 fell into two distinct states that appear to correlate with disease severity. State 2 identifies a more severe disease state than state 1, and a calculated probability of transition from state 1 to state 2 was estimated to be 100% [53]. Evaluating the MBS using these five parameters can potentially aid in assessment of the current disease state in a patient with GD2.

3.2.2 Skin ultrastructure—The enzyme GCase also regulates the ratio of ceramides to glucosylceramides in the outer layer of the skin, and lipid analyses have shown that stratum corneum from patients with GD2 have increased levels of glucosylceramide. In contrast, patients with both GD1 and GD3 have a higher concentration of ceramides which corresponds to that of control skin samples [54, 55]. Further electron microscopic evaluations of skin from patients with GD2 showed immature arrays of loosely packed lamellar-body derived membranes, contrasting with completely processed and orderly lamellar membranes seen in normal skin, as well as GD1 and GD3 skin samples [56, 57]. The unique electron-dense, non-lamellar phase interspersed within the immature lamellar membranes provides a potential means to distinguish GD2 skin ultrastructure from not only GD1 and GD3, but also X-linked ichthyosis and Niemann-Pick disease, another LSD [58, 59]. A more recent study examined epidermal biopsies of 20 different patients with GD2 in different stages of disease, all of whom exhibited this unique skin ultrastructure, further supporting skin ultrastructure as a potential method for discerning GD2 [60].

4.0 Diagnosing type 3 Gaucher disease

GD3 is especially heterogenous and is usually diagnosed on the basis of neurological manifestations associated with the GD presentation. However, GD3 encompasses multiple different phenotypes. While most patients with GD3 receive the diagnosis in childhood, we are now aware of some patients who are not identified until considerably later in life. Perhaps the most defining feature of GD3 is abnormal horizontal saccadic eye movements, although this sometimes is not appreciated, especially in young patients. The presence of this finding is very helpful in the diagnosis of GD3. And while three distinct subtypes of GD3 are currently described, it is likely that many more will follow. Furthermore, as treatments for the visceral manifestation of GD3 continue to increase patients' lifespans, patients may exhibit additional sequelae not previously reported with GD3.

4.1 Ophthalmologic findings

Different ophthalmologic manifestations are encountered in all GD types. Certain phenotypes present more often in a specific subtype, however, and can therefore provide insight into GD diagnosis.

4.1.1 Neuro-ophthalmologic findings—Neuro-ophthalmologic phenotypes can be found in both GD2 and GD3, although, the specific manifestations differ. In patients with GD2, squint and strabismus are common [3], although oculomotor apraxia and apraxia of eyelid opening can also be observed. Patients with GD3 almost uniformly exhibit slowing of the horizontal saccades and, less commonly, the vertical saccades [61, 62]. Typically, any slowing of the vertical saccades follows already slowed horizontal saccades, possibly suggesting an increased disease burden. Assessment of saccadic eye movements should be performed as a part of the clinical evaluation and have been used as a primary outcome measure in clinical trials due to their reproducibility and relatively easy quantification [63, 64]. Patients considered to have GD1 who develop slowing or looping of the horizontal saccades should be reevaluated and often recategorized as GD3 [65]. Therefore, ophthalmic findings can sometimes help discern between GD3 and GD1.

A recent study assessing saccades in patients with GD1 and GD3 using video-oculography found a subgroup of patients who were clinically diagnosed as GD1 with significantly slowed saccadic movement compared to healthy controls. These patients all shared the *GBA1* pathogenic variant p.R502C (R463C), and some had additional neurological features [66]. Thus, video-oculography may provide an additional diagnostic tool for physicians evaluating these patients.

4.1.2 White vitreous opacities—A recent clinical report examining a cohort of 30 patients with GD3, all with a genotype of L444P/L444P, revealed five patients who developed white vitreous opacities [67]. In this cohort, the presence of these white opacities correlated with more severe neurological manifestations of GD and a more rapid disease progression. The vitreous opacities have been shown to consist of “Gaucher cells” filled with glucosylceramide [68, 69]. These can be treated by removal of the vitreous and replacement with an appropriate fluid [70]. Although white vitreous opacities have been seen in patients with GD1, detailed eye exams remain important for patients with GD and appear to be more common in GD3 [71]. In addition, further exploration of therapies capable of crossing the blood-retinal barrier is needed, as continuous ERT treatment of patients with GD3 in this study did not prevent the formation of white vitreous opacities and subsequent visual impairment [67, 71, 72].

4.1.3 Corneal Opacities—The specific Gaucher genotype p.D448H/p.D448H (D409H/D409H) seen with GD3c is associated with cardiac calcifications, but corneal opacities have been reported in patients from a variety of GD centers [73–76]. Morphological assessment of the affected corneas showed abnormal rough endoplasmic reticulum and lipid profiles, thought to result from glucosylceramide accumulation in keratocytes. Taken together, this indicates that the cornea may serve as a potential marker for nGD as well as other lipid-related disorders [61, 77, 78].

4.2 EEG evaluations

A recent longitudinal cohort study in GD3 retrospectively evaluated the electroencephalograms (EEGs) of patients with GD3 [79]. This EEG study reviewed 293 EEGs collected from 67 patients over almost 50 years. More than 90% of the patients had at

least one EEG abnormality. Background slowing, seen in 90% of the patients in this cohort, was the most consistent finding, and may be helpful in identifying neurological involvement. Epileptiform discharges were documented in 54% of the patients, not necessarily associated with a clinical history of seizures. Data from these studies provides baseline information from a large GD3 cohort. An abnormal EEG and brain stem evoked potential (BSEP) is also a common finding in patients with GD2 [3].

4.3 Somatosensory and visual evoked potentials

Another non-invasive approach for evaluating central nervous system function is measuring somatosensory evoked potentials (SEPs) and visual evoked potentials (VEPs) [80–82]. An analysis of SEPs and VEPs from three patients with GD3 showed a high-frequency component and augmented amplitude in the VEPs and augmented amplitude in the SEPs compared to controls [83].

4.4 Longitudinal evaluation of cognition

Clinically, patients with GD3 vary greatly in their cognition, ranging from severely compromised individuals to high-functioning college graduates. A cohort of 34 individuals with GD3 was evaluated over time by a single neuropsychologist who performed IQ testing during a 29-year-long longitudinal study [84]. This study used an age-appropriate Wechsler Intelligence Scale to measure IQ and mixed-effects regression analysis to ascertain associations between IQ and clinical phenotypes. A remarkable span of IQ values was observed, ranging from a full scale IQ value of 39 to 125, with a mean value of 82. Verbal IQ values were consistently higher than performance IQ. The longitudinal analyses showed variation in IQ over time, with no discernable pattern or clear trajectory, demonstrating that GD3 is generally not a neurodegenerative disorder. Interestingly, the only clinical manifestations of GD3 found to be associated with IQ were EEG lateralization and behavioral issues. These results contrast from another GD3 cohort study of 34 Egyptian patients that found behavioral issues to be highly correlated with IQ, but not with EEG findings [85].

4.5 The progressive myoclonic epilepsy phenotype: GD3a

GD3a is typically distinguished by presenting with more severe neurological manifestations than GD3b, specifically, patients develop progressive myoclonic epilepsy [86]. Patients with GD3a do not exhibit a shared genotype, though in one study, variants p.N227S (N188S), p.G416S (G377S) and those derived from the pseudogene were found to be more common in the GD3a cohort, while p.L483P and p.R502C (R463C) were generally not associated with progressive myoclonic epilepsy [87]. There is also variability in both the age of onset and rate of disease progression within this population [87]. Even though the progressive myoclonic epilepsy phenotype was one of the first appreciated, further research is needed on GD3a that could have implications for both diagnosis and treatment [88]. Of note, mutations in *SCARB2*, the gene encoding the GCase transporter LIMP2, are also associated with syndromes including progressive myoclonic epilepsy [89]. In a unique family, where one child had mild GD1 and the second GD3a, a pathologic variant mutation in *SCARB2* was only found in the sibling with GD3a, appearing to serve as a genetic modifier [90]. However, pathologic variants in *SCARB2* were not observed in other patients with GD3.

4.6 The cardiac phenotype: GD3c

Patients with the pathogenic variant p.D448H/p.D448H (D409H/D409H) are considered to have GD3c. p.D448H is the second most common *GBA1* variant in Greece and the third most common in Spain; yet, homozygous individuals remain relatively rare [91–93]. GD3c was first described in patients from the Middle East, but there have been scattered reports from around the world. GD3c is uniquely characterized by cardiac involvement [94, 95], and the most common cardiac manifestations include calcification of the aortic and mitral valves and calcification of the aorta [74, 96, 97]. Additional cardiac phenotypes such as arrhythmias and fibrosis, atherosclerosis, and uncalcified stenosis of the aorta or valves have also been described [92, 98, 99]. In addition to the cardiac and corneal findings, some patients have been found to have hydrocephalus, pectus excavatum and/or other dysmorphic features. The mechanisms underlying GD3c are currently not understood, and the cardiac involvement and hydrocephalus seen are not responsive to enzyme replacement therapy.

Of note, there is a complex allele which includes both p.D448H and p.H294Q (H255Q) present in *cis* that is particularly common in Greece and the Balkans and is not associated with GD3c [100, 101]. In fact, homozygosity for this complex *GBA1* allele appears to be exclusively associated with GD2.

4.7 Lung and skeletal involvement in GD3

Both pulmonary and orthopedic involvement in GD3 are frequently described. When Gaucher cells form aggregates in the alveolar and interstitial spaces, this can result in interstitial lung disease which has been seen in these patients [92, 102]. CT imaging revealed parenchymal infiltrates in the lungs of patients with GD3, caused by infiltration of Gaucher cells in the alveolar and interstitial spaces. In a cohort of nine patients with GD3 evaluated by chest CT scans, two died of respiratory failure from interstitial fibrosis of the lungs [103]. While the interstitial lung disease can respond to ERT, the alveolar accumulations of Gaucher cells does not [102].

Skeletal involvement in patients with GD3 is common, and can be particularly severe in GD3b and the Norrbottnian subtype, but is rare in the GD3c subtype [104]. The skeletal manifestations can be the same as those seen in GD1: bone pain, bone crisis, osteopenia, osteosclerosis, osteonecrosis, and Erlenmeyer flask deformity [105]. Kyphosis and scoliosis have been described in patients with GD3 [106–108], but the mechanism is still unknown. Another finding reported is bilateral cystic lesions of the long bones in treated patients with genotype p.L483P/p.L483P [24, 109].

5.0 Treatment

One of the principal benefits of establishing the correct GD diagnosis is that it may impact management and treatment. The currently available therapies, while not impacting neurological outcome, can affect prognosis, longevity and quality of life.

5.1 Established Therapies

ERT has been the gold standard for treatment for Gaucher disease since the early 1990's [110]. Currently there are three preparations, imiglucerase (Cerezyme©, Sanofi-Genzyme, approved in 1994 [111]), velaglucerase alfa (Vpriv©, Shire-now Takeda, approved in 2010 [112]), and taliglucerase alfa (Eleyseo©, Pfizer, approved 2012), which are recombinant active forms of ß-glucocerebrosidase delivered through intravenous infusions. All formulations show similar efficacy, but differ in production methods, where both imiglucerase and velaglucerase alfa are produced in mammalian cells (Chinese ovary cells and fibrosarcoma cells respectively), and taliglucerase is produced in carrot root cells. However, no ERT crosses the blood-brain barrier (BBB), and while effective for most visceral signs of disease, the preparations do not address the neuronopathic features of GD. ERT is the standard of care for patients with GD3, for it greatly ameliorates the visceral and hematological manifestation and improves both quality of life and longevity.

Substrate reduction therapy (SRT), developed in the early 2000's, is a partial enzymatic inhibitor whose targets include glucocsylceramide synthase, which initiates the glycosphingolipid biosynthetic pathway and catalyzes the formation of glucocerebroside [113, 114]. Currently there are two approved drugs, both orally administered, 1st generation miglustat (Zavesca®, Actelion Pharmaceuticals-now Johnson & Johnson, approved in 2004), and eliglustat (Cerdelga®, Sanofi Genzyme). In a clinical trial, miglustat, while able to cross the BBB, was not found to be an effective treatment for neuronopathic GD (nGD) [64]. Eliglustat's side effect profile is better tolerated than its predecessor, earning a designation as first line therapy for untreated adults with GD1 with a compatible CYP2D6 profile [115, 116], but it does not reach therapeutic levels in the brain. Currently there is a phase 3 clinical trial evaluating eliglustat for use in pediatric patients ages 2–18 (Clinicaltrials.gov, NCT 03485677). There are also ongoing attempts to modify eliglustat to enable it to cross the BBB, but no clinical candidates at this time [117]. A newer SRT, Venglustat (Sanofi Genzyme), has been shown to cross the BBB [118]. It currently has completed several phase 1 clinical trials and it is currently under investigation for uses in GD3, Parkinson disease, and several other LSDs [119] (Clinicaltrials.gov, NCT02843035, NCT02906020, NCT04221451).

5.2 Emerging Therapies

Most disease-causing *GBA1* variants lead to missense or misfolded proteins, and chaperone therapy, chemical correction and stabilization of the defective proteins leading to correct translocation to the endoplasmic reticulum, has long been supposed as a possible treatment modality for GD [120, 121]. Many of these small molecule chaperones cross the BBB and may potentially treat nGD. There are several chaperones under investigation.

Ambroxol, a pH-dependent, mixed type inhibitor of GCase, was approved in the 1970s as a mucolytic and is found mostly in cough medicine in Europe and Asia [122]. Originally identified through a screening of over 1000 FDA approved compounds, Ambroxol has been shown to be maximally active at neutral pH levels in the endoplasmic reticulum and inactive in the acidic environment of the lysosome [123] and was thought to be a potential safe therapeutic adjuvant. Additionally, Ambroxol has been shown to increase GCase activity in

the brain of non-human primates [124]. There have been limited pilot studies of its use in patients with nGD with some anecdotal benefit, mainly suggesting improvement in the control of seizure frequency [125–127]. However, the lack of placebo-controlled studies makes *in vivo* efficacy difficult to determine. Current clinical trials are investigating its use in GD1 with poor response to ERT (clinicaltrials.gov, NCT03950050) and its potential efficacy in *GBA1*-related Parkinson disease (PD) and dementia with Lewy bodies (DLB) (clinicaltrials.gov NCT02914366, clinicaltrials.gov NCT04405596). Ambroxol is not currently approved for use in the USA.

Other inhibitory iminosugars, specifically N-(n-nonyl) deoxynojirimycin (NN-DNJ) [128], isofagomine (IFG) [129], have shown some potential as therapeutic chaperones, however, none have reached clinical trials. Chaperone therapy may be genetic variant-dependent, representing a therapy of the precision medicine era. Several new classes of non-inhibitory chaperones that are brain-penetrant including NCGC758 and NCGC607 have been identified [121, 130]. Optimized versions of these prototype compounds, identified by high-throughput screening of mutant enzyme, may have additional benefits.

Gene therapy has long been thought to be the therapeutic endgame for treatment in single gene Mendelian disorders, and it continues to be an avenue of research and promise in the GD field. There are several approaches under consideration, based on different delivery systems for the corrected genetic material. They have successfully treated different murine models of GD, including rescue of fetal mouse embryos, using a non-integrating adenovirus vector (AAV9 vector therapy) [131–133]. Integrating lentiviral vectors are another approach to gene therapy with efficacy shown in mouse models of GD [134]. There are currently clinical trials ongoing with both of these vectors. Prevail Therapeutics has launched the PROVIDE trial, an AAV9-based therapy, aimed at GD2 and is currently recruiting patients (clinicaltrials.gov, NCT04411654), while Avrobio is currently conducting the GuardOne trial, using a lentiviral-based therapy aimed at GD1 (clinicaltrials.gov, NCT04145037). Neither trial has been completed at the time of this review.

SapC-DOPS nanovesicles are a novel therapy to enable crossing of the BBB to enhance the function of mutant GCase. Saposin C (SapC) is a small lysosomal glycoprotein that along with augmenting GCase can protect GCase from degradation and inhibition by alpha-synuclein [135, 136]. SapC is encoded by the *PSAP* gene and variations leading to SapC deficiency present much like a GD phenotype[137, 138]. SapC has been coupled with the phospholipid dioleoylphosphatidylserine to create SapC-DOPs nanovesicles that were successfully used to deliver SapC to brain tumors of various origins, demonstrating the CNS selective ability of this approach [139, 140]. This therapeutic approach has been successful in rescuing nGD mouse models [141].

Another therapeutic approach being actively investigated is *in utero* enzyme replacement therapy (IUERT) which involves delivery of the recombinant enzyme via injections to the umbilical vein. Although our understanding of the development of the BBB remains incomplete, many studies over the past century have indicated its formation *in utero*, and therefore, administering ERT during pregnancy could allow for the drug to cross an immature, incomplete BBB [142]. Mouse models of the LSD Mucopolysaccharidosis type

VII (MPS7) have successfully been treated with IUERT [143], and an upcoming phase 1 clinical trial will recruit pregnant women carrying fetuses confirmed to have nGD to study the utility of IUERT in humans (clinicaltrials.ucsf.edu, NCT04532047). The utility of IUERT depends on reliable *in utero* diagnosis and poses ethical dilemmas such as saving a typically lethal phenotype that may produce a severely disabled infant.

5.3 When to Start Treatment

When to start treatment for Gaucher disease is a relevant topic for clinicians as well as for patients. Guidelines support the start of treatment when patients are 'symptomatic', such as in patients with abnormal hematological parameters, splenomegaly, bone crises and other manifestations of disease [144–146]. ERT generally results in amelioration of visceral disease, with most patients showing normalization of specific parameters within two years. Screening of asymptomatic pediatric patients with GD1 by assessing for changes or the development of disease manifestations should occur yearly [147]. The metabolic burden of GD can delay puberty, and as bone mass accrual occurs in the teen years, peak bone mass may not be achieved if treatment is delayed [148]. However, it is unlikely that nGD patients will fall into the asymptomatic category, as they usually show disease manifestations in either infancy or early childhood and initiation of therapy should be considered at diagnosis. Careful orthopedic evaluations should be performed in patients with nGD as there are reports of established pediatric patients that develop severe bone complications including avascular necrosis, despite being on high-dose ERT [107]. In nGD, close attention to the spine is recommended due to the high incidence of both kyphosis and scoliosis, which may require surgical correction [149].

The connection between *GBA1* variants and PD has been well established [150], with the lifetime risk currently of developing PD thought to be around 5–20% in patients with GD. There is also current literature suggesting that more severe *GBA1* variants correlate with an earlier onset and a more severe course of PD in affected individuals [151]. Should this prove to be true, as longevity for GD3 increases, these patients GD may be at increased risk. A recent case series reported four patients with GD3 who developed PD in the 4^{th} and 5^{th} decades of life [152]. It will be important to carefully monitor patients with GD3 for PD manifestations as they age.

GD2 remains a neurologically devastating disease, and treatment with ERT tends to be of limited therapeutic benefit due its inability to cross the BBB as discussed above. Therefore, recommendations regarding the use of ERT in GD2 is controversial [153]. Some argue that the therapy may provide comfort and ameliorate the distressing visceral manifestations of disease. A recent study capturing an updated natural history of this population observed that more aggressive management including ERT is prolonging life although not the neurological outcome [3]. Neurologic manifestations observed frequently in this cohort included choking episodes, myoclonic jerks, autonomic dysfunction, apnea, seizures, and diminished blinking, all of which worsened as disease progressed. Many affected infants received further assistive therapies such as gastrointestinal tubes (G-tubes), and tracheostomies [3]. Clear communication between provider and patients' family concerning treatment goals and outcomes is necessary to manage these patients.

6.0 Conclusion

Here, we detailed several emerging findings relevant to diagnosing and treating nGD. The diagnosis of GD2 should be considered whenever neonates present with hydrops fetalis or ichthyosis. Furthermore, swallow and skin ultrastructural evaluations may help distinguish patients with GD2 from other GD types. To discern whether patients have GD3, the evaluation should always include a neuro-ophthalmologic examination, specifically assessing for slowed horizontal saccades. Evaluations for pulmonary, cardiac, and skeletal involvement are also important, noting manifestations that might further indicate a specific subtype of GD3. EEGs can be helpful in documenting central nervous system involvement, in the absence of other metabolic processes. Neurocognitive assessments are also indicated in nGD and are useful for recommendations regarding educational strategies. Established therapies such as ERT and SRT can greatly impact visceral involvement in patients with nGD, and there is currently an effort to develop and investigate emerging therapies that could cross the BBB to potentially treat neurological manifestations of GD.

New developments in the field have ethical implications which can pose dilemmas for providers as well as for patients. Progress in genomic technologies have facilitated advancements in the diagnosis and treatment of GD. Infrastructure allowing for the continued treatment, monitoring, and support of patients diagnosed with GD is imperative to provide appropriate care. Such infrastructure, including genetic counselors, providers familiar with GD, and access to pharmacological therapies, are not dispersed equally across the globe. Researchers should therefore also investigate diagnostic and treatment modalities that can be implemented in lower-income countries. Continued study of current GD cohorts will further our understanding of this diverse disease, and ultimately improve the quality of life of patients with GD.

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- Patients with Gaucher disease (GD) are now being diagnosed earlier in life.
- Features of GD2 include abnormal swallow, stridor, hydrops fetalis, and ichthyosis.
- In GD3, expect slowed horizontal saccades and prominent visceral involvement.
- Small molecule chaperones and other brain-penetrant drugs are under development.
- There are ongoing gene therapy clinical trials targeting GD.

Table 1:

Features that may help in distinguishing GD2 from GD3

Feature	Suggestive of GD2	Suggestive of GD3
Genotype	p.L483P/null or null/null; p.D448H+ p.H294Q /p.D448H +p.H294Q	p.L483P/p.L483P; p.D448H/p.D448H
Presentations	Hydrops fetalis; Congenital ichthyosis; Organomegaly; Thrombocytopenia; Biliary atresia; Failure to thrive	Organomegaly; Anemia; Thrombocytopenia
Eye findings	Squint; Strabismus; Slowed or absent saccades (both horizontal and vertical	Slowed horizontal saccades; White retinal opacities; Corneal opacities (GD3c)
ENT	Stridor; Swallowing issues and related feeding difficulties (often described as ‘reflux’)	
Neuro findings	Opisthotonos; Hyper or hypotonicity; Seizures; Gross motor developmental delay; Loss of developmental milestones	Progressive myoclonic epilepsy; Learning disabilities; Hydrocephalus (GD3c)
Cardio-pulmonary	Aspiration pneumonias	Abnormal chest CT; Opacities on chest Xray; Calcification of cardiac valves (GD3c)
Bone	Kyphosis and/or scoliosis in infancy/young childhood	Kyphoscoliosis in childhood/adolescence; Bone cysts; Avascular necrosis; Pathological fractures

Although neuronopathic GD is a spectrum, some manifestations maybe more characteristic of either GD2 or GD3.