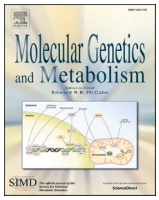
Molecular Genetics and Metabolism 145 (2025) 109124

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme



250 cases of "type 2 Gaucher disease": A novel system of clinical categorisation and evidence of genotype: Phenotype correlation

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ARTICLE INFO

Keywords:
Type 2 Gaucher
Neuronopathic gaucher
Genotype
Phenotype
Gaucher II

ABSTRACT

'Type 2' Gaucher disease, also referred to as 'acute neuronopathic' or 'infantile' Gaucher disease is an aggressive subtype of Gaucher disease, resulting from pathogenic variants in *GBA1*. The spectrum of phenotype ranges from hydropic perinatal presentations to an infantile disease characterised by rapid neurodegeneration. Increasingly, reports are offered of patients who survive into childhood, and it is unclear if these individuals represent a severe form of the type 3 (historically considered 'juvenile') disease or have modified outcomes resulting from contemporary medical interventions. Predicting outcome at point of diagnosis is increasingly important to families and clinicians, and while the impact of 'severe' or null alleles is appreciated, there remain significant uncertainties surrounding genotype-phenotype correlation.

In an era of clinical trials and endeavors to find CNS modifying therapeutics, there is a need to be able to categorise and predict clinical outcomes more accurately.

Here we report a case-series ($n = 13$) of internationally referred patients to a single centre, highlighting the spectrum of phenotype encompassed by the single nomenclature of 'type 2 Gaucher' disease. From this case-series we propose a new pragmatic, *clinical* classification system which could be applied to any infant at point of presentation. We subsequently applied this classification system to the historical literature and a further series of historical cases contributed by collaborators across the globe. We collated data from 250 cases, and demonstrate that it is feasible to apply this classification system and show that this has the potential to offer future genotype-phenotype correlation if expanded to a larger cohort.

1. Introduction

Gaucher disease (OMIM: 230800) is a lysosomal storage disorder resulting from pathogenic variants in *GBA1* which cause glucocerebrosidase deficiency. First described in 1882 [1], Gaucher disease was considered a systemic disease resulting in hepatosplenomegaly in adult

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https://doi.org/10.1016/j.ymgme.2025.109124
Received 23 February 2025; Accepted 21 April 2025
Available online 22 April 2025

patients. In 1927 the first case-series of infants with a neurological, rapidly progressive form of disease was described. This manuscript detailed four infants from a single family and collated the reports of a preceding six cases of infantile gaucher [2] with a severe neurological form of the disorder. The distinction of a new phenotype of Gaucher established clinical categorisation of type 1 and type 2 disease. The classification later expanded to included patients who were, described at the time as, 'juvenile onset' (type 3) with neurological features. These patients having a very clear phenotype in Sweden and often referred to as 'Norrbottnian'; subsequently identified as sharing a common genotype L444P/L444P (traditional allele nomenclature) (c.1448 T > C; p.Leu483Pro)) [3], now recognised as probably the most common *GBA1* variant. Our understanding of this broad-spectrum disease is ever expanding and has continued to expand with more global reporting in recent decades.

While the systemic manifestations of Gaucher disease can be effectively managed with enzyme replacement therapy (ERT) and in some, substrate reduction therapy (SRT), patients with neuronopathic disease (types 2 and 3) have persisting neurodegeneration which remains the greatest unmet need; to date, no therapeutic option has emerged which shows clear and consistent evidence of CNS disease modification.

Type 2 Gaucher disease (GD2) is perhaps the rarer of the subtypes, however this likely reflects the short lives of these infants, in the most severe forms, the diagnosis is often not made before the patient dies. Type 2 Gaucher disease is traditionally characterised by onset of neurological symptoms in infancy (before 6 months of age) [4] in the context of a biochemical and genetic diagnosis of Gaucher disease. Patients have a rapid but variable deterioration over a maximal duration of two years, with bulbar symptoms necessitating airway interventions e.g. tracheostomy and loss of swallow. Many infants develop motor and tone problems, and some evolve to develop seizures. The original descriptions from Oberling [2] described infants presenting at 5 months of age, or earlier, with significant growth failure, loss of visual attentiveness, strabismus, opisthotonus, increased tone, loss of ability to feed and death before 12 months with laryngospasm and asphyxia, and in some, myoclonus.

Type 3 Gaucher disease, while originally described as 'juvenile', usually manifests in infancy with a horizontal saccade defect, often strabismus and variable neurological features. It is clear however, that this phenotype is also a spectrum and evolution of neurological features later in adulthood is emerging [5] (distinct from the recognised parkinsonism associated with *GBA1* variants).

Following a review of referrals to our centre (local and international), we here report a case-series of patients and review the literature regarding the phenotypic spectrum of GD2, creating the largest ever single review of cases. While similar retrospective reviews have highlighted the heterogeneity of this population [6,7], we propose a more detailed *descriptive* classification. We apply this classification to the historical literature where sufficient clinical detail has been reported and in parallel, review the associated genotypes in this patient population. An ideal long-term outcome of this work, would be to enable genotype:phenotype correlation leading to earlier and more accurate prognostication for families. We show here that there is potential to achieve this with specific genetic variants but remain challenged by the common pan-ethnic L444P allele (C. 1448 T > G, p.Leu483Pro), which in homozygosity gives a neuronopathic phenotype of widely variable severity.

We hope to be able to utilise this classification for the benefit of families, to be able to offer a clearer prognosis and guide families to the risks and benefits of interventions. Clinical trials for this rare disease are active but by grouping all patients under the broad umbrella of 'GD2', given the heterogeneity of the disease and the emerging recognition of patients who straddle GD2 and GD3 classification [7], identifying comparable groups of trial patients limits trial outcome analysis and slows therapeutic progress.

2. Method

This study had three component parts; 1 – A case-series of thirteen patients referred to a single UK centre from across Europe; 2 – Collection of additional patient cases from referring clinicians and from historical UK databases; 3 – Review of the published literature to identify additional reported cases since 1990. Literature search used pubmed searching for the following key terms "gaucher type 2", "neonatal gaucher", "infantile gaucher", "perinatal lethal gaucher", "type II", "neuronopathic gaucher" and "neuropathic gaucher". Cases were included if data was provided on genotype and/or clinical presentation.

From reviewing our case series data, it was clear that all patients labelled as 'GD2' did not share a common phenotype, this allowed the proposal of a novel phenotypic classification which was then applied to the historical datasets (2 and 3 above). The subcategorisation and descriptions are detailed in Table 1.

No statistical methods were applied to this data which is descriptive only.

Genotypes are described as reported by referring clinicians or as documented in literature using contemporary nomenclature also, the A of the first AUG translation initiation codon is designated nucleotide $+1$[7] with traditional nomenclature allele names in parentheses (where amino acids are numbered with exclusion of the first 39 amino acids of the translated sequence) at first mention.

3. Results

The case series is presented in Table 2 with a column detailing how the proposed categorisation was applied to the cases.

Additional contributed cases totaled 51 patients (Table 2), with 15 of

Table 1
Proposed clinical categorisation of 'Gaucher Type 2'.

Gaucher-related Hydrops	Infants stillborn or born with collodion skin and hepatosplenomegaly, often contractures and evidence of hydrops; fluid accumulations e.g. ascites, heart failure, tissue oedema, effusions, polyhydramnios resulting in birth compromise. These infants are often born premature.
Neonatal Inflammatory	Infants presenting in the first month of life (usually the first week) with a hepatic involvement and evidence of generalised inflammatory response. These infants typically have severe thrombocytopenia, elevated inflammatory markers (e.g. ferritin) and established hepatosplenomegaly. Many have collodion skin/ichthyosis. They likely represent an attenuated hydropic phenotype previously referred to as 'lethal variant'
Neonatal Neurodegenerative (neuronopathic):	Infants presenting in the first month of life with a predominant neurological phenotype characterised by bulbar dysfunction, opisthotonos, mixed tone and movement disorder (typically spastic), dystonia.
Early Infantile neurodegenerative (neuronopathic):	Infants presenting before 6 months of age (but later than 1mo) with a predominant neurological phenotype characterised by bulbar dysfunction, laryngeal spasm and apnoea, opisthotonos, tone and movement disorders, often with seizures.
Late Infantile neurodegenerative (neuronopathic):	Infants presenting between 6 and 12 months of age with a predominant neurological presentation (in the presence of systemic/visceral Gaucher disease) but distinguished from GD3 by the presence of global developmental delay (although not excluding the possibility of making developmental progress) but with significant neurology before the age of two years e.g. seizure disorder. This cohort of patients are typically those referred to in the literature and the expert community as 'GD2/3' or '2–3 intermediates'.

Table 2
Case series of 13 patients with clinical subgroup categorisation.

Case Number	Genotype	Clinical summary	Outcome	Classification
1	Variant 1: c.470 T > G (p.IIE157Ser) *(L188S)* Variant 2: c.630C > T (p.(=)) Variant 3: c.1448 T > C (p.Leu483Pro), c.1497G > C (p.Val499Val), c.1483G > C (p.Ala495Pro) *(RecNcil)*	This infant was admitted directly to the neonatal unit at birth with ichthyosis; thrombocytopenia (16×10^9/L) and hepatosplenomegaly with AST peak at 442 U/L at day 3 of life. The neonatal period was managed with transfusions and treatment for presumed congenital herpes infection, prior to GD diagnosis. The infant stabilised with supportive care but had a further AST rise to 253 U/L at 3mo of age. The baby was hypotonic throughout and failed the newborn hearing assessment. Growth was poor and deterioration in feeding at 3 months of age coincided with increasing irritability. Strabismus and saccade impairment was clearly identifiable by 3 months of age. Acute illness accelerated a haematological picture of disseminated intravascular coagulation which was unresponsive to transfusion, resulted in a period of dependency on respiratory support prior to active palliative care at home.	Died at 4mo	Neonatal Inflammatory
2	Variant 1: c.1265_1319del (p.Leu422ProfsX4) Variant 2: c.1448 T > C (p.Leu483Pro) *(L444P)*	This infant presented at 4 months of age with respiratory distress and stridor, they had a history of back arching, and were found to have strabismus and hepatosplenomegaly. The infant was growth faltering. At presentation, platelets were 82×10^9/L and Hb 118 g/L. Abnormal liver enzymes were noted; ALT 43 U/L, AST 134 U/L and GGT 153 U/L. Acute respiratory infection with both COVID-19 and rhinovirus, resulted in need for invasive respiratory support and pediatric intensive care unit (PICU) admission. On discharge from PICU this infant was opisthotonic with paucity of lower limb movement. They had generalised hypotonia; stridor and excessive respiratory secretions. Swallow became unsafe and nasogastric feeding was necessary. Further deterioration in respiratory function resulted in need for non-invasive support and palliative care was delivered at home.	Died at 6mo	Early Infantile Neuronopathic
3	Variant 1: c.1448 T > C (p.Leu483Pro) *(L444P)* Variant 2: c.115 + 1G > A *(IVS2+ 1G > A)*	This infant presented at 5mo of age with breathing difficulties, symptoms of gastroesophageal reflux and significant growth faltering. They were recognised to have abnormal eye movements, generalised hypotonia, motor skill regression and episodes of hyperextension of the neck (early opisthotonos). Bilateral abducens palsy was recognised, platelet count was 122×10^9/L, ALT 80 U/L, AST 174 U/L. Between 5-7mo of age, feeding became increasingly difficult and secretions hard to manage. At 7mo, the baby experienced episodes of laryngospasm which resulted in hospital admission and GD diagnosis. At 9mo of age ERT and ambroxol were commenced and tracheostomy performed. A gastrostomy was sited to support feeding which offered some improvement in growth. A general improvement in development was seen but a parallel change in muscle tone with hypertonia peripherally, requiring baclofen for management. Slow developmental progress has been maintained and cochlear implants sited for hearing impairment. Periods of hospitalisation for respiratory support associated with intercurrent illness have been necessary. At 24mo nocturnal CPAP is used. At 38mo of age, seizures evolved which were initially difficult to differentiate from dystonia (but were captured with electroclinical correlate on EEG). At 43mo the child experienced osteonecrosis of the hip, this followed a femoral fracture at 22mo of age.	Alive age 3 yr 9mo	Early Infantile Neuronopathic/ Late Infantile neuronopathic
4	Variant 1: c.1342G > C (p.Asp448His) *(D409H)* Variant 2: del ex3-ex12	This infant was born to consanguineous parents who had experienced one previous fetal loss, and one previous death of a neonate at 15 days of life with a diagnosis of hepatitis and pulmonary haemorrhage (never tested for GD). This infant was diagnosed at birth following presentation with fulminant hepatic failure, thrombocytopenia (20×10^9/L) and massive hepatosplenomegaly. Ferritin was 4000 ng/ml at presentation with hyperbilirubinaemia. GD was diagnosed biochemically following exclusion of haemophagocytic lymphohistiocytosis (HLH) and the infant was commenced on weekly ERT infusions. Initially the child was fed via nasogastric tube but with resolution of hepatitis, they were briefly able to feed by bottle, and at 6 weeks had developed a responsive smile with no overt neurological compromise. The child became lethargic and less active, although ferritin had fallen to 600 ng/ml suggesting improvement in overall condition. An EEG was performed, which was normal, and a course of steroid therapy was commenced. Between 2 and 6 months the child primarily struggled with feeding and became reliant on nasojejunal tube support, they would experience autonomic symptoms during feeds, sometimes requiring oxygen therapy and experienced a series of asymptomatic febrile episodes. At six months there was evidence of interstitial lung disease and developmental delay.	ERT was stopped at 6.5mo and the infant died at 7mo of age	Neonatal Inflammatory
5	Variant 1: c.160G > A (p.Val54Met) *(V15M)* Variant 2: c.849C > (p.Tyr283*) *(Y244X)*	This infant was admitted to neonatal care from birth with a birth weight of 1.8 kg at 37 weeks gestation. Presentation was characterised by hepatosplenomegaly, anaemia and thrombocytopenia ($<30 \times 10^9$/L). Liver function showed ALT 210 mg/dl; AST 260 mg/dl. Clinical examination revealed ichthyosis, irritability and spontaneous clonus. Initially the infant was managed with blood product transfusions, these were no longer required following introduction of ERT from day 15 of life (platelets normalised following 2 ERT infusions, ERT given *weekly* at 60 units/kg *per dose*). Steroids (IV dexamethasone	Died at 4.5mo	Neonatal Inflammatory

(*continued on next page*)

Table 2 (*continued*)

Case Number	Genotype	Clinical summary	Outcome	Classification
		followed by oral prednisolone) were also given daily. Disease course was complicated by hypertension and hyperbilirubinaemia. At 3mo of age, further neurological deterioration was seen, primarily hypertonia, bulbar dysfunction with loss of swallow with subsequent respiratory compromise.		
6	Variant 1: c.84dup (p.Leu29Alafs*18) (*84GG*) Variant 2: c.1448 T > C (p.Leu483Pro) *(L444P)*	This infant presented at 5mo of age with dusky episodes related to apnoea. They were found to have thrombocytopaenia, anaemia, hepatosplenomegaly, and abnormal eye movements with strabismus. Liver function was normal. The infant progressed to develop profound episodes of laryngospasm requiring manual respiratory support. The infant experienced a bulbar deterioration with loss of swallow in parallel.	Died at 7mo	Early Infantile Neuronopathic
7	Variant 1: c.1448 T > C (p.Leu483Pro) *(L444P)* Variant 2: c.667 T > C (p.Trp223Arg) *(W184R)*	This patient had made early developmental progress but was found to have global neurodevelopmental impairment at 6mo associated with growth faltering. At 11mo they were admitted as an emergency following out of hospital respiratory arrest possibly associated with seizure. At evaluation, hepatosplenomegaly was identified, and GD diagnosis made. The infants' clinical course was complicated by episodes of laryngospasm, bulbar dysfunction necessitating gastrostomy insertion and active secretion management strategies.	Died at 14mo	Late Infantile Neuronopathic
8	Variant 1: c.115 + 1G > A (*IVS2 + 1G > A*) Variant 2: c.1256 A > C (p.Asp419Ala) *(D380A)*	This infant presented at birth with ichthyosis and respiratory distress secondary to laryngomalacia with a normal birth weight of 3.6 kg. They were admitted to intensive care at one month of age with laryngospasm which caused profound apnoea, tracheostomy was inserted. While hepatosplenomegaly was present, it was mild, and thus diagnosis of GD was a result of a generalised metabolic screen. At 6mo of age this infant was opisthotonic with ankle clonus and a mixed tone disorder; peripheral hypertonia and central hypotonia. The infant had both hearing and visual impairment but maintained some social interaction. Seizures occurred at 8mo.	Died at 8mo	Neonatal Neuronopathic
9	Variant 1: c.1448 T > C (p.Leu483Pro) *(L444P)* Variant 2: c.1289C > T (p.Pro430Leu) *(P391L)*	This infant, born with a birth weight of 2.5 kg at term, was admitted to the neonatal unit in view of ichthyosis and petechial rash. Initial lab results showed platelets of 35 × 10^9/L, ALT of 142u/L, cholestasis and coagulopathy. Moderate splenomegaly was identified on ultrasound and grade I bilateral intraventricular haemorrhages were noted on cranial ultrasound at day 2 of life. GD was diagnosed biochemically at day 8 of life. The infant received platelet transfusions on four occasions and FFP to reverse initial coagulopathy. Nasogastric feeding was commenced from birth given poor suck and compromised swallow. Growth was poor. Neurologically the baby showed a paucity of movement, episodes of irritability and, towards end of life, hypertonia. Death was preceded by two febrile respiratory illnesses, during both episodes the infant showed stridor and apnoea and required support with oxygen.	Died at 2mo	Neonatal Inflammatory
10	Variant 1: c.1342G > C (p.Asp448His) *(D409H)* Variant 2: c.882 T > G (p.His294Gln) *(H255Q)*	This infant was born at term (birth weight of 2.9 kg) and received their GD diagnosis at 1mo. The infant was investigated due hypertonia present in the first week of life, bulbar dysfunction with inability to swallow and subsequent growth faltering. Eye movement abnormality was identified early, and hepatosplenomegaly led to diagnosis. Laryngospasm occurred early in the disease resulting in prolonged episodes of apnoea. At 2mo of age the infant was irritable, described as encephalopathic and maintained an opisthotonic posture.	Died at 2mo	Neonatal Neuronopathic
11	Variant 1: c.1448 T > C; (p.Leu483Pro) *(L444P)* Variant 2: c.1505G > A; (p.Arg502GlnInFSx2) (*IVS10-1G > A (R463Q)*)	This infant presented at 7mo of age with global developmental delay but was able to sit unsupported. At initial assessment, hepatosplenomegaly was identified, leading to GD diagnosis and ERT was commenced. The infant had saccadic eye movement abnormality and generalised dystonia. At 8mo of age, seizures developed and over the subsequent months experienced increasing neurological compromise characterised by dystonia. No further gross motor milestones were achieved. At 16mo a gastrostomy was sited in view of bulbar dysfunction and at 18mo a tracheostomy insertion for management of recurrent episodes of laryngospasm. The infant gradually became dependent on respiratory support and evolved to experience refractory myoclonic epilepsy.	Died at 6 yrs.	Late Infantile Neuronopathic
12	Variant 1: c.1448 T > C (p.Leu483Pro)*(L444P)* Variant 2: c.1085C > T (p.Thr362Ile) *(T323I)*	This infant presented at 15 months of age with explosive onset of seizures, they were found to have thrombocytopenia and hepatosplenomegaly. The child had previously undergone strabismus surgery at 13mo following strabismus diagnosis at 6mo of age. They commenced ERT and ambroxol at 16mo of age. At 18mo, despite gross global developmental delay and profound saccade impairment, they continued to attain some developmental milestones, able to sit unsupported and beginning to pull to stand. The child has sensorineural hearing loss and communicates with single words, they are socially interactive. Epilepsy is controlled with the ketogenic diet.	Alive at 2 yr 9mo	Late Infantile Neuronopathic
13	Variant 1: c.1448 T > C (p.Leu483Pro) *(L444P)* Variant 2: c.653G > T (p.Trp218Leu) *(W179L)*	This infant presented at 5mo with global developmental delay and was found to have hepatosplenomegaly, strabismus, peripheral hypertonia and paucity of movements. They never achieved motor milestones beyond independent head support. At 6mo of age, swallow impairment necessitated nasogastric tube feeding.	Died at 8mo	Early Infantile Neuronopathic

these contributed by C. Mignot from their doctoral thesis and which may include *some* of the 15 patients excluded as described below.

From the historical literature search (since 1990); 201 cases were identified for inclusion (see Table 2). 15 cases [8], while they described clinical features of disease, a specific phenotype was not identifiable for each case and no genotype data was available (these 15 cases were reported by C Mignot and therefore are likely to overlap with the data provided from his thesis mentioned above), thus 186 were included in further analysis.

The data presented here of the combined case-series ($n = 13$), historical unpublished cases ($n = 51$) and published literature ($n = 186$) provides a cohort of 250 patients. Of these, genotype data was available for 223 cases, phenotype data was available for 227 patients and thus both genotype and phenotype data was available for 200 patients. Fig. 1 shows the distribution of cases by subcategorization.

Clinical classification was possible in 204 patients in total; in 19 the data was present but specific detail about the timing and nature of presentation wasn't provided with enough clarity to classify. The most frequent phenotype was early infantile however more late infantile patients may have been captured if greater interrogation of GD3 data was included. Fig. 2 shows probability of survival in months by phenotypic group. Hydropic infants are not shown, most died at birth, the longest surviving died at day 70 [9].

There were a total of 150 distinct genotypes, of these, 31 genotypes were seen twice or more and 18 had only one allele reported. 10 alleles were seen eight times or more and eight genotypes were seen three times or more (see Table 4). c.1448 T > C (p.Leu483Pro) (*L444P*) was the most frequent allele (accounting for 23 % of known alleles – see Table 2) and was present in 14 of the 31 repeated genotypes. L444P in trans with the common recombinant allele traditionally named RecNcil was seen 13 times and combined with the splice site variant IVS 2 + 1G > A in ten cases. Correlation with phenotype is shown in Table 3.

Variants were categorised by type, and genotypes examined for frequency by phenotype as shown in Fig. 3.

4. Discussion

Our recent experience of vastly different "Type 2" Gaucher patients, an observation shared globally [7], led us to consider a new way of classifying infants with severe clinical impairment resulting from Gaucher disease. The initial case-series demonstrates the variability in phenotypes, none of these patients shared genotype and although reported from a single geographical centre, are likely a good reflection of the global spectrum of disease, as patients were referred from across Europe and Asia.

We propose a classification reflective of other neuronopathic LSDs of infancy, describing patients by age at *symptomatic* presentation and nature of presentation (visceral or neurological). The rationale for selecting age at clinically significant symptoms, over age at diagnosis, simply attempts to correct for differences in investigative and diagnostic practices, newborn screening programs and screening as part of family planning in the context of family history. Similarly, identifying when symptoms became clinically significant (i.e. causing the infant impairment) may be distinct from the time at which they reach medical attention due to differential access to healthcare services. This classification does not rely on development of a specific symptom or age at death as these factors are modifiable with various interventions which again, are utilised differently around the world. The impact of interventions such as tracheostomy, enzyme replacement therapy and gastrostomy have complicated assessment and prognostication in this cohort of patients in recent years [10], this proposed classification is unburdened by these variables.

The spectrum of neuronopathic gaucher disease (both GD2 and GD3) is increasingly appreciated, especially with an increase in global reporting of patients [11]. Attempts have been previously been made to describe the GD2 spectrum [6], one system distinguished 'perinatal lethal', 'non-perinatal lethal' and 'intermediate' patients. However, if we applied this to our reported case-series, cases 9 and 10 would be indistinguishable. While hydropic infants, those with neonatal inflammatory and neonatal neuronopathic phenotypes are incredibly similar and probably represent a very closely related disease continuum, we need to be mindful of future therapeutic options. For example, case 4 in our series was treated with ERT and steroids early and there was clear evidence of visceral and inflammatory disease stabilisation, had a CNS-modifying therapeutic (e.g. a gene therapy) been available for this child, perhaps they would have been a suitable candidate. Conversely, case 10 (neonatal neuronopathic) would have been unlikely to benefit from steroids and ERT and so their management would always be different. The neonatal classifications are the most challenging to differentiate when considering age at presentation alone, however, as is

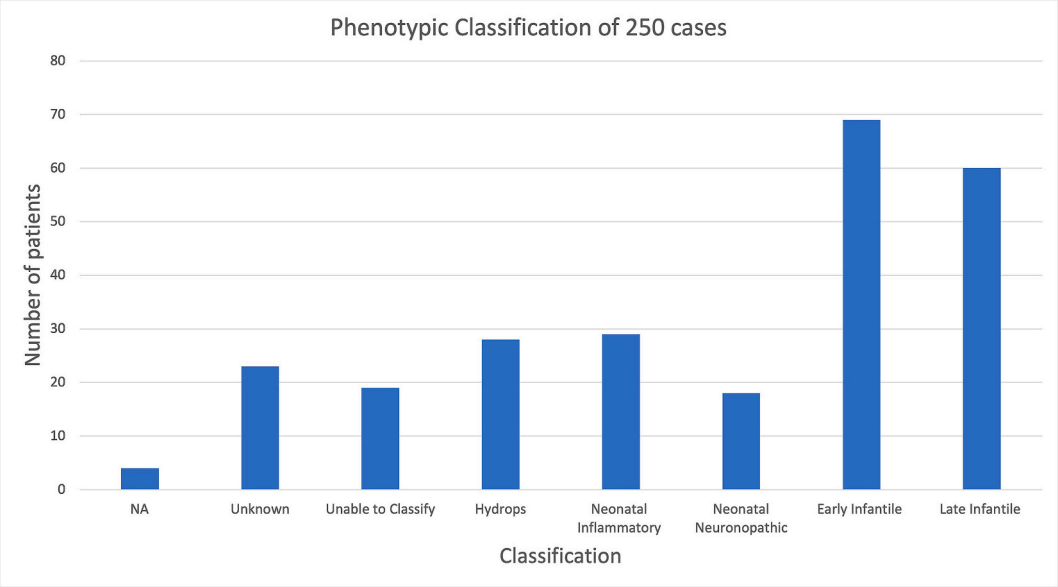

Fig. 1. Bar chart showing number of patients in each phenotypic classification.
Note: NA applies to cases included which were derived from patient cell lines only.

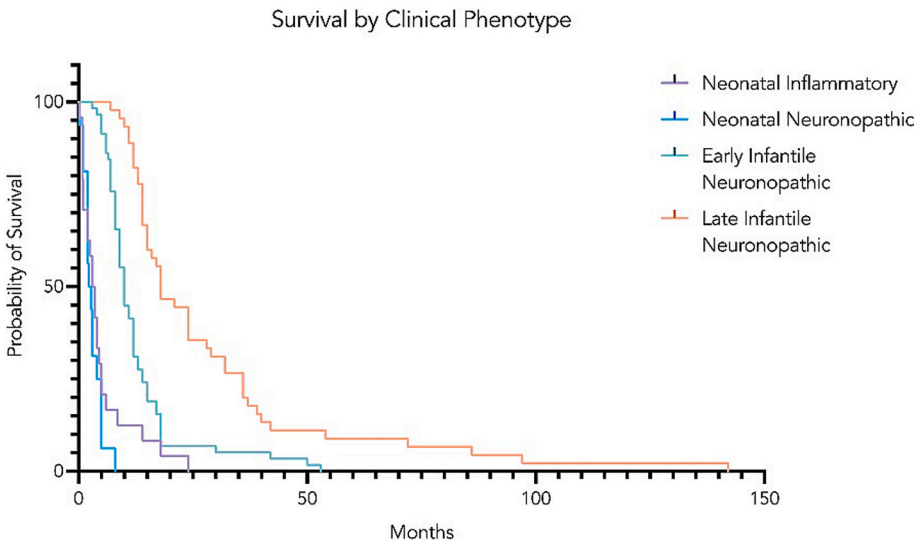

Fig. 2. Survival graph showing probability of survival of infants (in months) by clinical phenotype.

demonstrated by the example cases provided, the clinical characteristics are quite distinguishing between the two disease forms.

We propose five GD2 subclassifications which clearly reflect a disease spectrum. Distinguishing hydropic, inflammatory and neonatal neuronopathic patients is quite challenging from historical literature where there are multiple shared clinical features. Traditionally many of these patients would have been referred to as 'perinatal lethal variant' and while this is an accurate descriptive, it is an uncomfortable term to use with families and doesn't inform management other than to prompt palliation. The neonatal neuronopathic patients were often those patients born with immediate movement disorder and seizures in the context of ichthyosis and hepatosplenomegaly. These patients possibly represent a fractionally more severe phenotype than those with inflammatory disease, characterised by high ferritin, liver disease (and usually loss of liver function) and frequent non-infective febrile episodes. These latter infants become irritable and develop neurological manifestations if they survive the first few months of life.

The nomenclature we selected is considered to be clinically descriptive and clinically useful. While 'congenital' might be preferred to 'neonatal', the intent was to describe the infant at presentation, and it would be fair to assume that all of the subgroups have an ongoing disease process from birth (and probably earlier). The decision to describe infants with visceral disease, liver failure and ichthyosis as 'inflammatory' reflected the observation that several infants present as

Table 3
Frequencies of alleles in cohort of 251; table shows those alleles which recurred >5 times.

Allele	Frequency (n)	Frequency (% of known alleles)
c.1448 T > C (p.Leu483Pro)*(L444P)*	98	22.9
c.1448 T > C (p.Leu483Pro), c.1497G > C (p.Val499Val), c.1483G > C (p.Ala495Pro) *(RecNcil)*	38	8.9
c.1342G > C (p.Asp448His) *(D409H)*	25	5.8
c.721G > A (p.Gly241Arg) (*G202R)*	19	4.4
c.115 + 1G > A (*IVS2 + 1G > A*)	16	3.7
c.754 T > A (p.Phe252Ile) (*F213I*)	16	3.7
c.887G > A (p.Arg296Gln) (*R257Q)*	14	3.3
c.1342G > C + c.882 T > G (p.Asp448His) + (p.His294Gln) *(D409H + H255Q)*	10	2.3
c.1448 T > G (p.(Leu483Arg) (*L444R*)	9	2.1
c.508C > T (p.Arg170Cys) (*R131C*)	8	1.9
c.475C > T (p.Arg159Trp) (*R120W*)	7	1.6
c.1448 T > C; c.1483G > C; c.1497G > C; C*92G > A	7	1.6
c.1085C > T (p.Thr362Ile) (*T323I*)	6	1.4
c.667 T > C (p.Trp223Arg) (*W184R)*	6	1.4
c.1263del55 (p.Leu422ProfsX4) (*Rec55*)	5	1.2

Table 4
Recurrent genotypes, frequency and correlation with phenotype.

Genotype (traditional nomenclature)	Frequency in cohort	Phenotype
L444P / RecNcil	13	**Early Infantile n = 7** Late Infantile n = 3* Cell line n = 1 Unable to classify n = 2
L444P / IVS 2 + 1G > A	10	**2 patients* [15] *'presented' at 7mo and died by 12 and 13mo may be better classified as EI* **Early infantile *n* = 7** Unknown*n* = 3*
L444P / G202R	6	**2 patients* [11] *presented at 4mo but no clinical description provided – likely EI phenotype* Early infantile *n* = 1* **Late infantile n = 5**
RecNcil/RecNcil	5	**patient described as presenting at 1mo but survived until > 4 yrs more consistent with a LI phenotype* Hydropic n = 4 Late infantile *n* = 1*
D409H + H255Q / D409H + H255Q	5	**Contributed from thesis* Early Infantile n = 1 **Neonatal Inflammatory *n* = 2** **Neonatal Neuronopathic n = 2**
L444P / T323I	5	Late infantile n = 3 Early infantile n = 1* Unknown n = 1
L444R / L444R	4	**diagnosed at 10mo – possibly a late infantile patient* Neonatal Inflammatory n = 1 Neonatal neuronopathic n = 2 Unable to classify n = 1*
RecNcil / F213I	4	**either NI or NN* **Late Infantile n = 4**

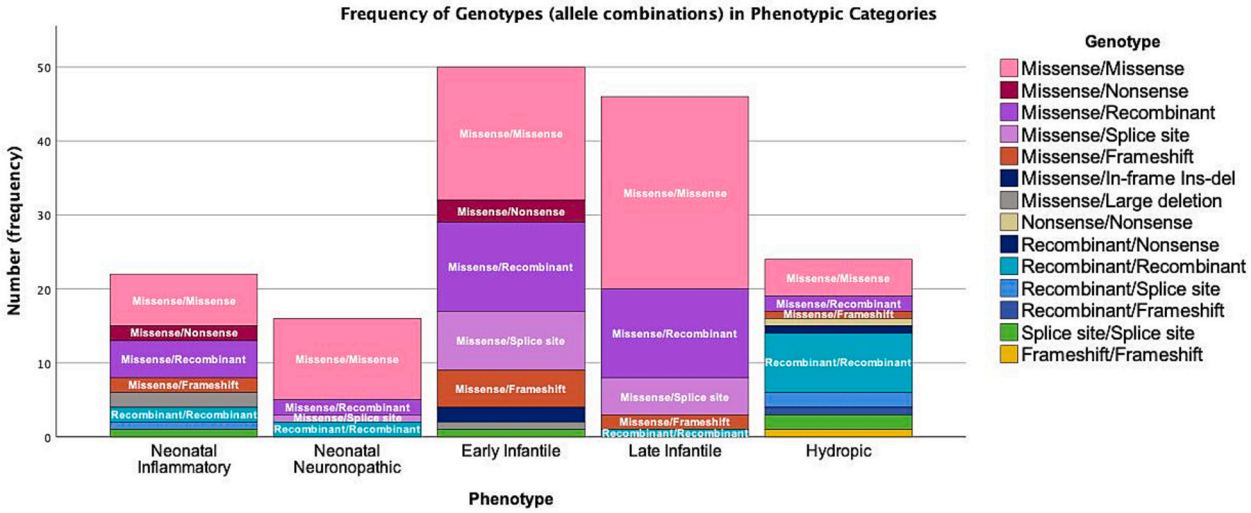

Fig. 3. Graph showing frequency (number) of 'types' of allele combinations e.g. Missense/recombinant by different phenotypic categories.

Haemophagocytic Lymphohistiocytosis (HLH)-mimics with acutely elevated inflammatory markers (e.g ferritin). That is not to say that this form of Gaucher disease is distinctly more inflammatory than any other form of Gaucher disease but to help clinically in making accurate diagnosis, offering prognosis and directing interventions.

Early infantile and late infantile neuronopathic subtypes are primarily distinguished by the age at which they present, however the late infantile patients often continue to develop some developmental skills, while still grossly deviating from typical neurodevelopmental trajectories. Progressive bulbar impairment is common in both but occurs much earlier and often more rapidly in the early infantile cohort, culminating in a dramatic episodes of laryngospasm and apnoea. Interventions can be utilised to modify survival outcomes (tracheostomy, gastrostomy etc) however overall Gaucher disease burden progresses even with all available interventions and therapies utilised, as demonstrated by case 3.

Possibly the most challenging group here are the late infantile patients when considered in the context of GD3. In the UK Gaucherite cohort of GD3 patients ($n = 42$) [12], the median age at presentation was 2y (almost half diagnosed between 12-24mo). Of those patients who presented in infancy, five patients with the most severe disease had global developmental delay. Some of those patients could therefore have been described, within this proposed criteria as late infantile GD2. As such, we would propose abandoning the terms GD2 and GD3 and simply referring to patients as 'neuronopathic Gaucher disease'. Distinguishing a late infantile neuronopathic Gaucher patient from a classical neuronopathic (GD3) patient would be on the basis of the burden of neurological involvement before the age of two years. Given that we have here reported a total of 108 pathogenic variants in *GBA1* (with >500 reported to date), there will always be patients who are more challenging to categorise or whose disease course is divergent from expectations and in whom prediction of phenotypic outcome using genotype in isolation will not be possible.

An ideal classification would utilise objective data, such as genotype and possibly a biomarker. To date genotype:phenotype correlation in GD more broadly has been limited to a small number of common, well characterised variants. N409S (c.1226 A > G, *N370S*) for example, is a variant only ever seen in non-neuronopathic disease [13], common to the Ashkenazi Jewish population and while neuroprotective in regards to neuronopathic disease, has been implicated in Gaucher-related Parkinson's disease. In GD3, there is emerging data consistent with 'more severe' variants in heterozygosity, including recombinant variants, as more likely to result in a neuronopathic phenotype. The most challenging of genotypes is the L444P (c.1448 T > C (p.Leu483Pro)) homozygous genotype, the most common genotype in GD3, and with a very broad phenotypic spectrum. Groups continue to explore this variant and postulate the impact of modifiers to expression, the contribution of the upstream almost identical pseudogene (in which this variant occurs at a site of high recombination incidence) and the variable protein expression of the pseudogene in different cells. Interestingly in this cohort, the L444P variant was only seen in early infantile and late infantile patients, with the exception of five cases (despite being the most common variant overall); two hydropic infants with W184R (c.667 T > C (p.Trp223Arg)) on the opposing allele and three neonatal inflammatory patients, one with a recombination, one a multi-exon deletion and one with P391L (c.1289C > T (p.Pro430Leu)) in trans.

Historically, *GBA1* variants have been categorised as 'mild', 'intermediate', 'severe' or 'null' [14] and the expert community will often evaluate a genotype based on the combination of allele severity. In the context of GD2 and a new classification, all variants are 'severe' or 'null' and so the genotypes need to be interrogated in much greater numbers which is challenging in an ultrarare disease.

We were able to see several genotype-phenotype correlations within this dataset, demonstrating that a genotype:phenotype correlation is *feasible* and should be interrogated in larger studies. The methodology here has limitations, we reviewed historical data from over 30 yrs., an era where genomic analysis has advanced significantly and where analysis has not been fully described or confirmed in parents in many cases. Furthermore, *GBA1* analysis is particularly complex, due to the presence of the highly homologous pseudogene; there will be inevitable genotype inaccuracies which will subsequently effect the genotype: phenotype evaluation we have attempted. While there were challenges with applying the novel phenotypic classification to published literature, particularly where there lacked clarity about when symptoms became clinically significant, it was possible to do so. Achieving this on the basis of such small amounts of data, is a strength of the proposed system and suggests it could be utilised globally clinically, irrespective of resources.

We have provided the largest single review of patients with GD2 offering both a clinical and genetic analysis. We have shown it is possible to identify genotype:phenotype correlations using a novel but simple clinical categorisation of patients at point of presentation. This system offers a platform for future clinical studies and genotype:phenotype analysis. We hope it can be utilised to identify the most appropriate candidates for therapeutic interventions and clinical trials.

Ethics approval & patient consent

No project-specific ethical approval was required for this study which evaluated the existing literature, and a patient cohort referred to a single site. Cases contributed by external collaborators obtained family consent where able and/or confirmed the contributions as per their local ethical procedures. Ethnicity and country of origin of the contributed cases are specifically not provided to maintain anonymity of patients.

CRediT authorship contribution statement

A. Donald: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **S. Brothwell:** Data curation, Writing – review & editing. **B.M. Cabello:** Data curation, Investigation. **C. Ehrstedt:** Data curation, Investigation, Writing – review & editing. **J.R. Fernández-Fructuoso:** Data curation, Investigation. **E. Fernández-Marín:** Data curation, Investigation. **D. González-Lamuño:** Conceptualization, Data curation, Investigation. **J.M. Lloreda-García:** Data curation, Investigation. **L. Lykopoulou:** Data curation, Investigation. **C. Mignot:** Data curation, Investigation, Resources. **J. Nurse:** Data curation, Investigation, Writing – review & editing. **S. O'Sullivan:** Data curation, Investigation. **A.N. Persson:** Data curation, Investigation. **J. Raiman:** Data curation. **D.S. Rajan:** Coneptulization, Data curation, Investigation. **J. Uberos:** Data curation, Investigation. **S.A. Jones:** Conceptualization, Data curation, Formal analysis, Resources, Supervision, Writing – review & editing. **H.J. Church:** Data curation, Formal analysis, Resources, Writing – review & editing.

Funding

The first author is funded through the NIHR (as an academic clinical lecturer) but the study did not receive any other funding.

Declaration of competing interest

Authors AD, SAJ, DSR are investigators in the Prevail (Lilly) PROVIDE clinical trial in GD2. Authors AD and SAJ have provided consultancy and received honoraria for travel from Sanofi, Takeda and Avrobio. SB has also received travel honoraria from Takeda.

Acknowledgements

The authors would like to acknowledge the families who consented to the sharing of their child's data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2025.109124.

Data availability

The datasets used in this study may be available with restrictions to some details (for patient confidentiality) from the corresponding author on reasonable request.

References

[1] P. Gaucher, De l'épithélioma primitif de la rate. Hypertrophie idiopa- thique de la rate sans leucémie, Thèse de médecine. (Paris), 1882.
[2] Charles Oberling, Pierre Woringer, La maladie de Gaucher chez la nourrisson, Extra. Rev. Franc. Pediat. 3 (1927) 475–532.
[3] N. Dahl, M. Lagerström, A. Erikson, U. Pettersson, Gaucher disease type III (Norrbottnian type) is caused by a single mutation in exon 10 of the glucocerebrosidase gene, Am. J. Hum. Genet. 47 (1990) 275.
[4] R. Schiffmann, et al., The definition of neuronopathic Gaucher disease, J. Inherit. Metab. Dis. (2020), https://doi.org/10.1002/jimd.12235.
[5] A. Donald, et al., Eye movement biomarkers allow for the definition of phenotypes in Gaucher disease, Orphanet J. Rare Dis. 15 (2020) 349.
[6] N. Gupta, I. Oppenheim, E. Kauvar, N. Tayebi, E. Sidransky, Type 2 Gaucher disease: phenotypic variation and genotypic heterogeneity, Blood Cells Mol. Dis. 46 (2011) 75–84.
[7] O. Goker-Alpan, et al., Phenotypic continuum in neuronopathic gaucher disease: an intermediate phenotype between type 2 and type 3, J. Pediatr. 143 (2003) 273–276.
[8] C. Mignot, D. Doummar, I. Maire, T.B. De Villemeur, Type 2 Gaucher disease: 15 new cases and review of the literature, Brain Dev 28 (2006) 39–48.
[9] H. Adachi, A. Noguchi, S. Ota, T. Takahashi, H. Nanjo, Bronchoalveolar lavage fluid in an infant with perinatal lethal Gaucher disease, Pediatr. Int. 59 (2017) 636–637.
[10] T. Roshan Lal, et al., The natural history of type 2 Gaucher disease in the 21st century, Neurology 95 (2020) e2119–e2130.
[11] D.L. Stone, et al., Glucocerebrosidase gene mutations in patients with type 2 Gaucher disease, Hum. Mutat. 15 (2000) 181.
[12] S. D'Amore, et al., In-depth phenotyping for clinical stratification of Gaucher disease, Orphanet J. Rare Dis. 16 (2021) 431.
[13] E. Sidransky, Gaucher disease: complexity in a "simple" disorder, Mol. Genet. Metab. 83 (2004) 6–15.
[14] E. Beutler, T. Gelbart, C.R. Scott, Hematologically important mutations: Gaucher disease, Blood Cell Mol. Dis. 35 (2005) 355–364.
[15] L. Kang, et al., Genotypes and phenotypes in 20 Chinese patients with type 2 Gaucher disease, Brain Dev. 0 (2018).