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# Gaucher Case Report with Intermediate Type 2-3 Phenotype: Light and Shadows in the Era of NBS

**Mohn A, Maggitti A*, Ingrosso D, Polidori N, D'arcangelo A and Chiarelli F**

Department of Pediatrics, University of Chieti-Pescara "Gabriele D'Annunzio", Chieti, Italy

***Corresponding author:** Alessandro Maggitti, Department of Pediatrics, University of Chieti-Pescara "Gabriele D'Annunzio", Via Vestini, Chieti, Italy, Tel: 3899408039

## Abstract

Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder (LSD) caused by a deficiency of the lysosomal enzyme acid β-glucosidase (GCase), encoded by the GBA gene. GD is classified into three types based on the absence (GD1) or presence and severity (GD2 and GD3) of involvement of the nervous system. However, these distinctions are not absolute, and it is increasingly recognized that neuropathic GD represents a phenotypic continuum where a genotype–phenotype correlations is often not conclusive. In the last years, several states, including Italy, have settled pilot screening programs for selected and most frequent LSDs, with the intent to provide valuable guidance for risk stratification and clinical management, despite the costs and the ineffectiveness of ERT in specific subtypes of GD and others LSDs. Herein, we report a pediatric case of GD with an intermediate type 2-3 phenotype, diagnosed in 2000, when extended NBS wasn't available yet, and with a novel mutation on a single allele never previously described in literature (T231R).

## Introduction

Gaucher Disease (GD) is an autosomal recessive lysosomal storage disorder caused by a deficiency of the lysosomal enzyme acid β-glucosidase (GCase), encoded by the GBA gene. Since now, more than 400 of biallelic pathogenic variants of GBA gene have been described [1]. Very rarely, GD can also be caused by a deficiency in the GCase activator, saposin C. However, GCase deficiency leads to an accumulation of its substrate, glucosylceramide, in mononuclear-phagocyte lineage cells and other tissues, such as nervous system, resulting in damage to multiple organ systems. Although considered a rare disease in the general population, GD is the most prevalent

lysosomal storage disease [2]. GD has a wide range of diverse clinical manifestations that have been well distinguished, based on extent and age at onset of neurological involvement: type 1 (GD1, chronic non neuronopathic), type 2 (GD2, acute neuronopathic) which leads to death in the first years of life, and type 3 (GD3, chronic neuronopathic), a slowly progressive neurovisceral form [3]. Type I GD is mainly characterized by splenomegaly, hepatomegaly, thrombocytopenia, anemia, growth retardation and various bone manifestations, with an onset ranging from childhood/adolescence to adulthood. Children with GD2 typically have prenatally or perinatally systemic and neurological manifestations, and usually die before the age of 3 years [4]. Individuals with GD3 have similar systemic involvement to those with GD1 (though often more severe), but neurological impairment that may manifest over time, such as epilepsy, ataxia, spasticity, vertical and horizontal gaze paralysis, and dementia [4]. Despite this accurate characterization, patients are often incorrectly diagnosed or experience significant delays in receiving an accurate diagnosis [5], with a delay >7 years in almost one in six patients, reported by a recent survey by Mehta et al [6]. The availability of the Enzyme Replacement Therapy (ERT) since the early 1990s has changed the natural history of GD, using a recombinant form of glucocerebrosidase. ERT is recommended for all patients with symptomatic GD1 and GD3. The most recent recommendations have assessed that ERT is ineffective on the progressive course of acute neuronopathic GD2, given its inability to cross the blood-brain barrier by systemic route of administration [7]; however, evidence suggests that ERT off-label use may be helpful for palliative management of GD2 [8]. Moreover, the recent oral Substrate Reduction Therapy (SRT), which decreases glucocerebroside (GlcCer) production, is approved only for GD1. In the last years, several states have settled pilot screening programs for selected LSDs, including Italy [9,10], with the help of tandem mass spectrometry (MS/MS) methods to analyze proteins and substrates in Dried Blood Spots (DBS). Burlina et al [9] first demonstrated the feasibility and effectiveness of screening programs for LSDs in Italian newborn population. Due to genotypic heterogeneity, genotype–phenotype correlations in GD are often not conclusive, and the introduction of Newborn Screening (NBS) may be helpful to provide valuable guidance for risk stratification and clinical management [5]. Herein, we report a pediatric case of GD with an intermediate type 2-3 phenotype, diagnosed in 2000, when extended NBS wasn't available yet, and with a novel mutation on a single allele never previously described in literature (T231R).

## Case Presentation

A 9-month-old child presents with hepatosplenomegaly and low-grade fever (37.3-37.5°C). After excluding other causes (hematologic malignancy, histiocytosis, infections) and considering the significant clinical picture, a bone biopsy was performed. This revealed increased cellularity, with the three hematopoietic lines being normally represented and in regular ratios. An infiltrate of histiocytic-type cells with filamentous cytoplasm was observed; these findings were indicative of a storage disorder. Consequently, suspecting a metabolic disease, the patient was referred to a specialized pediatric metabolic diseases center. At this referral center, suspecting Gaucher disease, plasma chitotriosidase levels were measured, revealing elevated values (17760 nmol/ml/h; normal value <350). Additionally, low levels of β-glucosidase (1.9 nmol/ml/h) were

confirmed in peripheral leukocytes. An Auditory Brainstem Response (ABR) test was performed, showing a mild-to-moderate brainstem conduction delay. Considering the previously performed bone biopsy and the clinical-anamnestic picture (hepatosplenomegaly, global developmental delay with hypotonia, poor muscle trophism, psychomotor integration deficits, and saccadic eye movements), the suspicion of Gaucher disease intermediate between type II and type III was confirmed. Genetic testing identified a single mutation, T231T (not described in the literature at the time of diagnosis), and no mutation was found on the second allele. The genotype did not allow for determining the disease course to modulate the therapeutic approach before the development of more severe symptoms. Additionally, it did not permit differentiation between type II or type III. Enzyme replacement therapy with high-dose homologous β-glucocerebrosidase (100 U/kg/month) was initiated at one year of age. A clinical and laboratory follow-up was scheduled every 6-8 months to assess the treatment's evolution and efficacy.

## Clinical Course and Progression

At the first clinical follow-up, 6 months after initiating treatment, an improvement in neurological development was observed, although hepatomegaly persisted. Blood tests showed a reduction in chitotriosidase levels (9520 nmol/ml/h). An Auditory Brainstem Response (ABR) test was repeated, confirming a moderate conduction delay. At the subsequent follow-up, the patient exhibited delayed acquisition of postural control and language development. Physical examination revealed mild hepatomegaly, with the spleen palpable under the costal margin. Follow-up blood tests showed a further reduction in chitotriosidase levels (4000 nmol/ml/h). The ABR showed improved conduction but still a slight delay. The current therapy was continued. At age of 3 years the patient achieved ambulation with support. Physical examination showed persistent mild hepatomegaly. Further reduction in chitotriosidase levels was noted (1800 nmol/ml/h). At the next follow-up (at age of 4 years), the neurological age appeared comparable to the chronological age. The patient presented with hypertonia, marked hyperreflexia, ataxia, oculomotor apraxia, dysarthria, and supported ambulation. Given the persistent delay in psychomotor milestones, a bone marrow transplant was proposed. After being informed of the risks and benefits, the parents decided to decline the procedure. Despite the progressive reduction in chitotriosidase levels (780 nmol/ml/h), due to the neurological condition, continuation of enzyme replacement therapy at a doubled dosage, as recommended by a second specialist center, was prescribed (240 U/kg/2 weeks). Periodic follow-ups, including MRI of the spine and hip joints, showed no involvement of the bone marrow. At age of 5-6 years with the new dosage of the medication, the patient showed improvement in neurological development with recovery in motor milestone acquisition, though oculomotor apraxia and wide-based gait persisted. However, the patient began experiencing recurrent infections, including an episode of basal right posterior bronchopneumonia (BCP); frequent herpetic infections around the periauricular and periocular areas requiring antiviral therapy; an episode of otomastoiditis due to sinusopathy; and a periauricular Pseudomonas infection complicating another herpetic exacerbation. At age of 7 and a half years old, the patient had a height below the 3rd percentile and a weight between the 25th and 50th percentiles. The patient exhibited normal mental development and appropriate schooling

(second grade). There was a confirmed significant overall clinical improvement and reduction in hepatosplenomegaly. Subsequent follow-ups (8-10 years) showed a slight increase in chitotriosidase levels (1670 nM/h/mL), but with evidence of good metabolic and clinical compensation of Gaucher disease. The patient demonstrated nearly normal intellectual development, with slightly limited motor development due to the wide-based gait. During the follow-up, the patient never experienced bone crises or hematologic involvement. Additionally, bilateral sensorineural hearing loss was detected, leading to the recommendation for hearing aid application. Continuation of enzyme replacement therapy with Cerezyme was confirmed. At the age of 11, the patient experienced a first tonic-clonic seizure (afebrile). The episode began with generalized tremors and a fall to the ground without loss of consciousness, followed by loss of consciousness, generalized hypertonia, and a fixed gaze. The episode lasted approximately 3-4 minutes. Upon admission, the patient was in fair general condition with a negative neurological examination. He was hospitalized for further evaluation. An EEG revealed multiple parieto-occipito-temporal anomalies. A cranial CT scan was normal, excluding the presence of space-occupying masses, signs of intracranial hypertension, and/or hemorrhage. Incidentally, probable signs of chronic sinusopathy with calcifications were noted. Blood tests were not significant, with normal complete blood count and liver and kidney function. ECG was normal. The child did not experience any seizures during hospitalization and was discharged with recommendations to minimize exposure to bright lights and maintain a regular lifestyle with an appropriate number of sleep and wake hours. Micronoan enemas (10 mg) were prescribed for use in case of another episode. In agreement with the parents and the secondary-level metabolic diseases center, it was decided to forego anticonvulsant therapy, in accordance with contemporary guidelines (reference needed).

At the subsequent follow-up, plasma chitotriosidase levels were found to be decreasing (931 nM/mL/h; normal value <100). Considering the auxological parameters, the patient's height and weight were below the 3rd percentile. Given the stability of the clinical condition and the absence of bone involvement, it was deemed unnecessary to add other medications to the enzyme replacement therapy. It was advised to lower the Cerezyme dosage to 60 U/kg every 2 weeks, as there was no evidence that higher doses (120-480 U/kg every 2 weeks) were more effective than moderately high doses, according to studies from that period. At the age of 11-12 years, the patient experienced a second seizure episode. In agreement with the specialized secondary-level center managing the patient, it was decided to initiate antiepileptic treatment. During the treatment, the patient continued to experience seizure episodes (3-4 per month) characterized by tremors followed by rigidity of all fr limbs, loss of consciousness, and ocular retroversion, lasting several minutes, mostly occurring at night. In some cases, rectal diazepam was administered when the seizures appeared to last longer. Despite the combined antiepileptic therapy, the patient remained refractory to treatment. At the age of 13-14 years, the patient demonstrated good intellectual performance, despite necessitating significant educational support, ultimately achieving success by winning a poetry contest **(Table 1)**.

**Table 1:** Award-winning poem (SENTO…SOGNO…/I'M FEELING…I'M DREAMING).

***mesi sono volati***
***le stagioni sono passate***
***ed io non ho sentito.***

***Sono passate davanti ai miei occhi***
***Feste, cerimonie e baldorie.***

***Quanto sarebbe bello sentire, udire e ascoltare….!***

***Qual è il danno che ho fatto***
***per portarmi appresso questo masso?***

***Per fortuna la scienza, la tecnologia e la chirurgia si sono fatte avanti***
***ora posso sentire discorsi, schiamazzi e canti.***

***Senza gli aiuti forniti non vivrei,***
***non ce la farei a perdermi***
***tutto quello che porta, nel nostro mondo,***
***la gioia di sentire!***

***Ora posso sentire***
***ma, per mia sfortuna, sento cose sconcertanti,***
***che provocano molti danni***
***facendo vergognare tutto il mondo.***

***Comunque l'angoscia è passata:***
***posso sentire….. ma non smetto di sognare.***

***Sogno una vita migliore,***
***piena di gioia e senza dolore.***

***Sogno una vita di uguaglianza***
***fra giovani e vecchi, donne e uomini***
***fra sani e malati, ricchi e poveri***
***dove il potere non esiste***
***e viviamo tutti in pace e in armonia con la natura***
***sentendo i suoni e ammirando la sua bellezza.***

***Sogno una vita migliore***

***dove viviamo tutti insieme con un senso di fratellanza.***

***Questo lo sogno…..***

***questo lo sento.***

Months have flown by
the seasons have passed,
and I haven't heard.

They passed before my eyes,
festivities, ceremonies, and revelries.

How wonderful it would be to hear, to listen, and to understand…!

What damage have I done
to carry this burden with me?

Fortunately, science, technology, and surgery have advanced,
now I can hear conversations, shouts, and songs.

Without the aids provided, I wouldn't live,
I wouldn't manage to miss
verything that brings, in our world
the joy of hearing!

Now I can hear,
but, unfortunately for me, I hear disconcerting things,
that cause much harm,
making the whole world ashamed

However, the anguish has passed:
: I can hear... but I do not stop dreaming.

I dream of a better life,
full of joy and without pain.

I dream of a life of equality
equality between young and old,
between the healthy equality, between young and old

where power does not exist
and we all live in peace and harmony with nature,
the sounds and admiring its beauty.

I dream of a better life
where we all live together with a sense of brotherhood.

This I dream...
this I feel.

***D.C. N.,I sez. A Liceo Socio-Psico-Pedagogico "Gonzoga" di Chieti***

## Deterioration and Sedation

At the age of 15, the patient exhibited further neurological deterioration, necessitating hospital care. At that time, the patient's condition was marked by significant neurological impairment, including pharmacoresistant myoclonic epilepsy, bilateral sensorineural hearing loss, dysarthria, bradykinetic-ataxic syndrome, ichthyosis, and visual deficits. Transient dysphagia for liquids also emerged. It was decided to continue Cerezyme at a dosage of 60 U/kg every 15 days intravenously, with a gradual discontinuation in preparation for the introduction of Zavesca, as discussed with the parents. Over the following year, the progressive deterioration of the patient's general and neurological conditions, with frequent recurrent seizures, necessitated palliative pharmacological sedation, respiratory physiotherapy (PEP mask), and continuous enteral nutrition. Enzyme replacement therapy was discontinued at the age of 16.

## Discussion

It's becoming increasingly clear that all types of GD present a wide spectrum of phenotypic variation and genotypic heterogeneity. Our patient indubitably represents part of this continuum; the molecular characterization identified a novel mutation on a single allele (Ex 7, T231R - 809C>G), then reported in the GBA analysis in Italian Gaucher patients by Filocamo et al **[11]** in 2002, and so far undetected in other populations ever again. Although it has been suggested that genotype plays a main role in determining the degree of neurologic involvement **[12]**, the mechanisms of a strict genotype-phenotype correlation still remain unclear, given the influence of other multiple factors, such as environmental influences, genetic modifiers and epigenetics **[13-20]**. Our data show that the phenotype observed could not have been predicted from the surprising genotype. Furthermore, despite the inexorable progression of neurologic involvement typical of GD2, our patient had normal language and cognitive skills, and he attended school with good performance until he could. By far, ERT was effective in delaying many systemic manifestations and cognitive deterioration, and in avoiding severe bone pain (bone crisis). Poor growth, described in the literature **[14]**, might be the only skeletal manifestation of the disease in this patient. Despite being a neuropathic form (type II-III), the treatment with ERT seems to have also improved the patient's psychomotor and cognitive development. Conversely, literature describes ERT as generally ineffective for neurological conditions and often

not recommended (especially for type II) [15]. However, there are other studies that demonstrate how, in selected cases of type III, high doses of ERT can impact the progression of the disease [17]. Suspecting that the recurrent infections might be due to a possible immunological depression related to Gaucher disease, the possibility of a bone marrow transplant was considered. It is a curative treatment but is associated with high morbidity and mortality rates (citazione). The lack of consistent data from recent years raises the suspicion that bone marrow transplantation may now be reserved only for a limited number of cases. Based on the anamnesis, clinical and laboratory data, an immunodeficiency was excluded by the specialized center. He died during adolescence and still represents one of the oldest patient described in literature with similar phenotype [12]. But inevitably the question arises: what would that have changed 20 years later in the era of NBS? We believe that an unequivocal answer is not possible. Certainly, NBS presents several technical and ethical challenges. The uncertainty of diagnosis and the awareness that in many LSD pathologies it is not possible to achieve a benefit in slowing disease progression limit its broader implementation. The accuracy of screening tests is progressively improving, allowing for the minimization of false positives [19]. In addition to expensive costs, some authors have claimed that NBS for LSDs has some drawbacks, such as the diagnosis of asymptomatic individuals who may experience the disease after years (especially GD1), not knowing the timing of ERT introduction and of the clinical-laboratory follow up [18]. For GD1 forms, NBS is critically important; early diagnosis and subsequent early initiation of therapy are crucial for preventing significant bone sequelae [21]. Moreover, even with an early diagnosis, severe subtypes of GD2 detected with NBS may not benefit from early ERT, due to its substantial inefficacy on nervous system involvement. The importance and utility of NBS could be amplified by the introduction of new treatments, currently under investigation, that are more effective on the central nervous system [22]. On the contrary, expanded NBS programs and the resulting genotypization would certainly help to more characterize the subphenotypes of the disease.

## Conclusion

NBS could become a crucial tool in the future with the introduction of new therapies that are more effective in addressing neurological progression and the refinement of techniques, ensuring improved quality of life and increased survival for patients. Specifically, a stronger phenotype-genotype correlation would be desirable for the proper management of these patients **(Figure 1)**. Currently, despite significant advancements, the implementation of NBS remains insufficient for LDS, and in particular GD. Therefore, we highlight the need for larger cohorts of GD patients in the literature, which would provide better guidance for risk stratification and clinical management. Our case report broadens the phenotypic-genotypic understanding of Gaucher disease, presenting a severe phenotype in heterozygosity, further complicated by a previously undescribed mutation. This expansion of phenotypic-genotypic knowledge could facilitate accurate genetic counseling within the framework of neonatal screening programs for lysosomal storage disorders. This case would be an additional contribution to the complex phenotype-genotype correlation in Gaucher Disease.

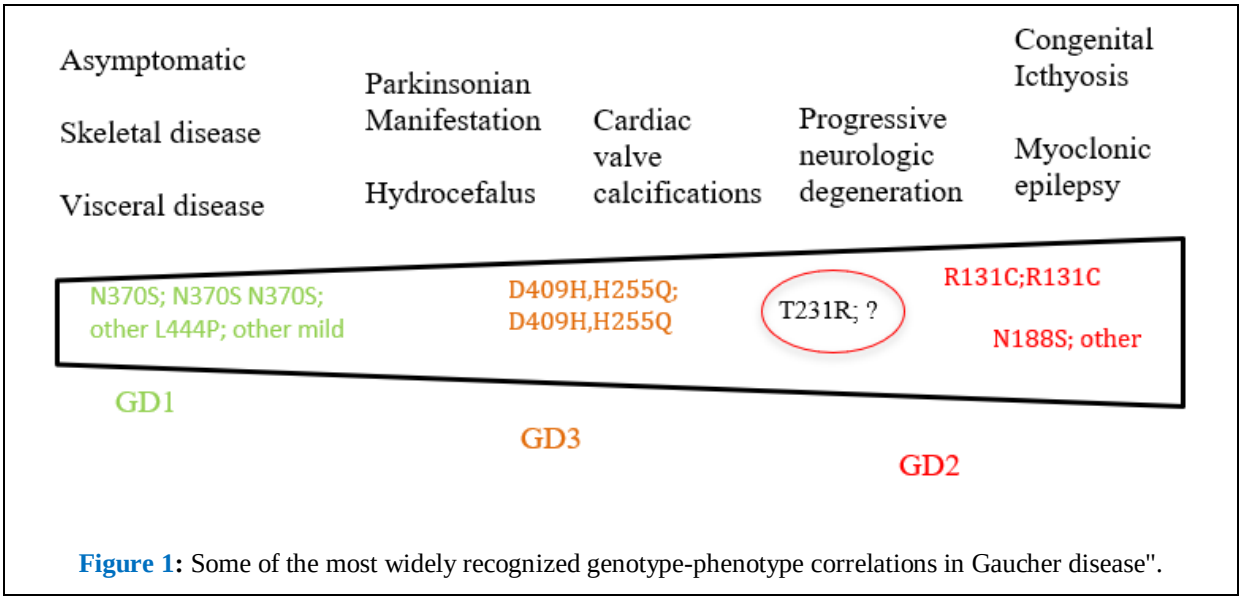


**Figure 1:** Some of the most widely recognized genotype-phenotype correlations in Gaucher disease".


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