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Neuronopathic Forms in Subjects with Mutations in *GBA* Gene

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1. Introduction

Gaucher disease (GD) (GD, OMIM 230800), is the most common glycosphingolipid storage disorder, with an estimated global prevalence of 1:200,000 of the population (Cox & Schofield, 1997). Impaired activity of the lysosomal enzyme, β -glucocerebrosidase, leads to build-up of glucosylceramide in macrophages, forming dysfunctional, lipid-engorged 'Gaucher cells' that accumulate primarily in the liver, spleen, bone, lungs and nervous system (Grabowski & Horowitz, 1997; Beutler, 1997). Figure 1 Sometimes, bone disease or cellular infiltration in bone marrow, could be lead to fractures or hematomas that cause neurological complications from compression of the spinal cord or peripheral nervous system. In addition, severe deficiency of β -glucocerebrosidase increases the accumulation in the central nervous system of glucosylceramide and other toxic metabolites in the neuronopathic involvement. However the precise mechanisms by which glucosylceramide storage originate them is still unclear. The frequency of neurological GD cases is ranging between 7% and 17%, according to different series (Biegstraaten et al., 2008; Chérin et al., 2010).

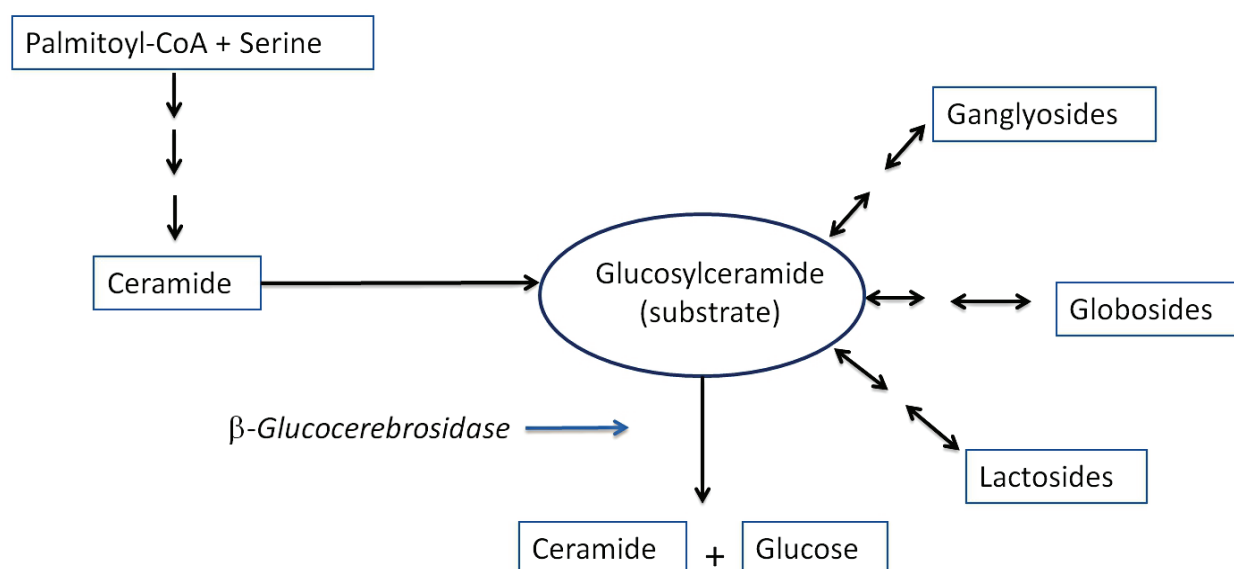


Fig. 1. Biosynthesis and degradation of sphingolipid

2. Clinical characteristics of neurological forms

The neuronopathic forms of GD can be either acute type 2 (GD2) (MIM 230900), or chronic type 3 (GD3) (MIM 231000), the presence of neurological symptoms is the main characteristics for a diagnosis, nevertheless in a low percentage of type 1 GD (GD1) some neurological manifestations could be considered part of the GD1 phenotype.

These forms are considered as ultrarare and estimated at about 5% for GD3 and 1% for GD2 (Charrow et al., 2000).

2.1 Type 2 Gaucher disease

There are many descriptions of type 2 Gaucher disease presenting with hydrops fetalis and joint contractures. In the majority of cases with this severe phenotype, glucocerebrosidase activity is absent or severely deficient. In general, most patients with Gaucher disease do have some residual glucocerebrosidase activity, with no correlation between severity and the level of residual enzyme activity.

The patients with the acute form, usually die within two years. The initial neurological symptoms as paralysis of horizontal gaze supranuclear are followed later, with strabismus, impaired vertical gaze, dysarthria, difficulty in swallowing, chewing, laryngeal stridor and a pyramidal syndrome with opisthotonos. Some of these patients develop a progressive encephalopathy that is neocortical in origin. The molecular and cellular bases for the phenotypic variation and the progression of the neuronopathic features in Gaucher disease are poorly understood. Few studies are available from human tissues that correlate neuronopathic progression, pathologic involvement, and the clinical manifestations. To fill this void, several mouse models with GCase null or point mutations or chemical inhibition were developed. The GCase-null mutations exhibited a defective skin permeability barrier, similar to that in collodion babies. Skin permeability barrier defects lead to death shortly after birth and have limited their utility in understanding the pathogenesis in CNS of type 2 and 3 Gaucher disease (Xu et al, 2008)

2.2 Type 3 Gaucher disease

The patients with chronic form, GD3, the first neurological symptoms usually appear at a mean age of 8 years, and the patients with myoclonic epilepsy variant by age 15 (Park et al., 2003) in these cases the life expectancy can reaches the third decade. Nevertheless, there have been reported some cases of apraxia of gaze without progression to other neurological symptoms (Kraoua et al., 2011). There are other GD3 subtypes, GD3b, the neurological involvement is limited to apraxia of the eyes, but is associated with visceral enlargement and bone disease. (Patterson et al., 1993). Other less common GD3 subtype, have been classified as 3c characterized by heart valves calcification and eye movement disorders (Chabas et al., 1995).

The GD3 has heterogeneous clinical manifestations, and therefore different subtypes have been referred. GD3 subtype a, is characterized by apraxia of gaze and dementia associated with myoclonic epilepsy, ataxia and extrapyramidal signs or spasticity. In addition in this subtype there are several specific forms including the myoclonus epilepsy as the main manifestation (Park et al., 2003). These neurological forms have slight or moderate visceral involvement and bone changes are characterized by chest deformities and kyphoscoliosis, which may have a neurological basis, however bone crises normally are absent (Tylki-Szymańska et al., 2010).

2.2.1 Myoclonic epilepsy

Different lysosomal storage diseases: late-onset GM2 gangliosidosis, type 2 GM1 gangliosidosis, Niemann-Pick disease, sialidosis, galactosialidosis, pseudodeficiency of arylsulfatase A, Gaucher disease and some forms of ceroid lipofuscinosis have been associated with myoclonic epilepsy (Tinuper et al., 1994; Kowarz et al., 2005).

The main form is an association between Gaucher disease and myoclonic epilepsy in a rare subgroup of patients with GD type 3 who developed a progressive myoclonus epilepsy. All had horizontal saccadic eye movements. The lack of a shared genotype for patients and the variability in clinical presentations suggesting the existence of other modifying factors contributing to this rare phenotype (Park et al., 2003). Have also been documented cases in Spanish population with symptoms of myoclonic epilepsy (Giraldo et al., 2011). In a study of a Spanish patient with neuronopathic type 3 GD and myoclonic epilepsy symptomatic improvement was observed using a combination of substrate reduction therapy with enzyme replacement therapy (Capablo et al., 2007).

Although the mutation N188S in the *GBA* gene in Gaucher disease was initially considered a mild mutation or a variant modifier has been reported the association of this mutation with the development of myoclonic epilepsy, suggesting that the enzyme could lead to abnormal death of neuronal cells or modify the role of other proteins involved in epilepsy (Kowarz et al., 2005). In recent years, understanding the genetic basis of myoclonic epilepsy has progressed rapidly and several defects have been identified, specific genes and mutations (Scheffer & Berkovic, 2000, Stafstrom et al., 2000, Delgado-Escueta et al. 2001). Recently genes have been identified for other forms of progressive myoclonus epilepsy:

- a. The *CLN3* gene has been associated with a type of neuronal ceroid lipofuscinosis, Batten disease, contains 15 exons and spans over 15 Kb. The International Batten Disease Consortium isolated the gene *CLN3* between microsatellite markers D16S288 and D16S383 on chromosome 16p12.2.1-16p11 (International Batten Disease Consortium, 1995). It is speculated that the gene product functions as a chaperone involved in folding / unfolding or assembly / disassembly of other proteins, specifically the subunit c of ATP synthase complex (Janes et al., 1996). Biochemically mutation causes multiple deficiencies in the enzyme complexes of the respiratory chain involving NADH-CoQ reductase (complex I) in the cytochrome C oxidase (COX).
- b. A mutation at nucleotide 8344 of human mitochondrial DNA causes MERRF (Myoclonus Epilepsy Associated with Ragged-Red Fibers) (Shoffner et al., 1990).
- c. The gene for cystatin B (*CSTB*) is located on chromosome 21 in a segment of about 175KB, between D21S2040 and D21S1259. Expands into three exons over 2500bp, encoding a small protein of 98 amino acids. Mutations in the gene encoding cystatin B are responsible for primary defect in patients with progressive myoclonus epilepsy type Unverricht-Lundborg (EPM1) autosomal recessive (Pennacchio et al., 1996). The encoded protein is a member of the superfamily of cysteine protease inhibitors (Jarvinen & Rinne, 1982, Turk & Bode, 1991).
- d. *EPM2A* gene is located on chromosome 6q24 and contains 5 exons that encode two laforin isoforms, isoform A is located in the rough endoplasmic reticulum and isoform B in the nucleus. Laforin is a dual specificity phosphatase and functions are involved in protein degradation by the proteasome (Lohi et al., 2005) and glycogen metabolism (Worby et al., 2006). Mutations in the gene *EPM2A* cause deleterious effects on protein encoding the laforin, causing Lafora disease, which is an autosomal recessive progressive myoclonic epilepsy (Minassian et al., 1998).

3. Histological changes in neurological forms

The neuropathological studies (Wong et al., 2004) in patients with different types of GD have found clear pathologic changes in several areas of the brain, mainly in the form of perivascular Gaucher cells, astrogliosis and neuronal loss. Immunohistochemical findings in the same study suggest that, in certain areas, elevated intracellular levels of glucocerebroside would further reduce glucocerebrosidase levels and contribute to cytotoxicity as well as to abnormalities in calcium homeostasis and increased sensitivity of neurons, thus facilitating spontaneous neuronal discharges. More recent data reinforces the role of cytotoxic molecules, but possibly related to the intraneuronal accumulation of the defective enzyme (Futerman; 2006). It has also been proposed that the accumulation of glucosylsphingosine, is responsible for the neurological symptoms (Pelled et al., 2005). On the other hand, the finding that mutation N188S may be associated with the development of myoclonic epilepsy, suggests that the abnormal enzyme might lead to neuronal cell death, or modify the role on other proteins involved in epilepsy (Kowarz et al., 2005). Neuropathological exam in a GD3 patient suggests that cerebellum-dentate degeneration would play a major role in these patients' myoclonus (Verghese et al., 2000). How this relates to in vivo cortical dysfunction is unclear. Probably, other factors in addition to point mutations, environmental, epigenetic and genetic, will ultimately be involved in the development of myoclonic epilepsy in GD patients.

In some cases of myoclonic epilepsy an improvement in neurological symptoms have been observed with substrate reduction therapy (SRT), the biochemical basis of this improvement could be related with small molecules that have been shown to enter the CNS both in animal models and in patients and this was an important argument maybe related to the reduction of glucocerebroside accumulation by the substrate reduction activity. It could also be related to the described chaperoning effect on the defective glucocerebrosidase or a functional improvement, through a yet unknown mechanism, in the defective calcium homeostasis described above (Pelled et al., 2005).

4. Clinical characteristics of type 1 Gaucher Disease

Classically, GD1 is characterized by organomegaly, cytopenias, bone disease and absence of neurological manifestations. However, there are several reports of the co-occurrence of neurological problems, as a consequence of spinal cord or nerve compression following vertebral body collapse or bleeding within confined compartments (Grewel et al., 1991). There is accumulating evidence that in a few GD patients, prominent neurological abnormalities may become evident during adult life (McKeran et al., 1985). Several new lines of evidence have implicated an association between GD and the development of parkinsonism. The first hints of a relationship between the two disorders were suggested by scattered case reports of patients with Gaucher disease who developed early-onset, treatment-refractory parkinsonism (Neudorfer et al., 1996; Machaczka et al., 1999; Tayebi et al., 2001). In a clinic-based series of Parkinson disease patients from Israel, (Aharon-Peretz et al., 2004) screened for the most frequent mutations in glucocerebrosidase gene, they identified 31% with glucocerebrosidase mutations including three N370S homozygotes. This frequency was at least fivefold higher than the observed in their two control groups used.

In an international collaborative study conducted in sixteen countries with 5961 patients with Parkinson disease in all ethnic groups, compared with 4898 controls, the odds ratio estimated for any type of *GBA* mutation has been of 5.43 (Sidransky et al., 2009).

We have studied the characteristics of Gaucher disease in Iberian Peninsula. The Iberian Peninsula (IP) is located in the extreme Southwest of Europe and includes the states of Portugal and Spain. It is the second-largest peninsula in Europe, with an area of 580,000 square kilometers and with a total 55 million of inhabitants. The actual IP genetic pool has been influenced by many major populations and immigrations, including the Paleolithic Iberian population, which already existed by 50,000 B.C. Later, by North Africans who entered the Iberian region between 20,000 and 8,000 B.C. and by the Saharans, who arrived between 8,000 and 4,000 B.C. In addition, there were also people coming from central Europe (also generically called Celt invasions), during the first millennium B.C. At the beginning of the 8th century Islamic peoples (generically called Arabs) entered Spain (Arnaiz Villena et al 1999, C rte-Real HB et al 1996). Taking into account all these data, nowadays it is believed that, the timing of divergence of populations within Iberia points to a shared ancestry of all populations in the Upper Palaeolithic. Further genetic subdivision is apparent in Catalonia and Andalusia, with increased genetic diversity in the latter. Lineage diversity comparisons of IP populations with European (Tuscan) and North African (Algerian) populations shows the Iberian Peninsula to be more similar to other European populations, although a small number of Iberian lineages can be traced to North Africa.

Since the early 70s, the group of Dr. Chabas in Barcelona (Spain) and the Dr. Sa Miranda in Porto (Portugal) has been dedicated to the identification and study of lysosomal storage diseases including GD (Cormand et al. 1995, 1998; Amaral et al 1993). Moreover since 1993, the Spanish Foundation for the Study and Treatment of Gaucher Disease (FEETEG) keeps the Spanish Registry of GD (SRGD) and also coordinates the screening, diagnosis, characterization, treatment, and follow-up of GD patients in Spain (Giraldo et al. 2000, Alfonso et al 2007).

Of the 436 subjects included in this series, the 96.1% were born in Iberian Peninsula, Balearic and Canary Islands, 92 patient were from Portugal (21.1%) and 327 (75.0%) Spanish origin and 17 were immigrants (3.9%). Patients born at IP were classified at diagnosis: 370 as GD type 1 (88.3%) (age mean: 40.6 ± 20.30 years, range 0.3–87); 28 as GD type 2 (6.7%) (Age: mean 0.4 years, range 0–1) and 21 as GD type 3 (5.0%) (Age: mean 5.9 years, range 2–17). Mean age at diagnosis in the total GD patients was 26.3 ± 19.88 years (range 0–87) and 28.7 years in patients type 1. To date, 63 patients from IP in this series are death (15%) and 373 are alive (85%). According the type distribution 7.6% of type 1; 52.4% of type 3 and 100% of type 2 are death.

4.1 Association of Parkinsonism with Gaucher disease

Parkinson disease (PD), the second most common neurodegenerative disorder after Alzheimer's disease, has a complex and multifactorial etiology, with different contributions: genetic, epigenetic and environmental. It can be classified by age of onset as early PD or late PD and in the form of presentation as family or sporadic PD.

The main clinical phenotype of Parkinson's disease is characterized by motor dysfunction such as bradykinesia, tremor at rest, rigidity and postural instability, but can also affect autonomic functions and knowledge (Poewe, 2008).

The prevalence of the disease is associated with age, and is approximately 1 in 100 individuals at 65 years and increasing to 4–5% at the age of 85 years (Van den Eeden et al., 2003).

Parkinson's disease is mainly due to a progressive degeneration of dopaminergic neurons in the substantia nigra and other monoaminergic cell groups of the brain (Braak et al., 2003),

resulting in increased microglial activation and accumulation of proteins in the surviving dopaminergic neurons, known as Lewy bodies and Lewy neurites (Forno, 1996). Symptoms appear when between 50-70% of nigrostriatal dopaminergic neurons are lost.

Although Parkinson's disease has been considered a genetic disorder of not sporadic origin, only 5 to 10% of patients show monogenic forms of the disease. Some genes are associated with Parkinson's disease, and several of them are presented in an autosomal dominant or autosomal recessive.

Autosomal dominant: PARK1/ α -sinucleín, PARK4/ α -sinucleín, PARK8/Leucine-rich repeat kinase 2 (LRRK2) and microtubule associated protein tau (MAPT).

Autosomal recessive: The PARK2 gene is located on chromosome 6q25.2-q27 and comprises 12 exons with intron structure superexpanded of 1.3 Mb of genomic DNA, which encodes a protein of 465 amino acid N-terminal domain similar to ubiquitin. Mutations in the parkin gene (PARK2) were identified for the first time in several Japanese families with autosomal recessive juvenile parkinsonism (Kitada et al., 1998).

PTEN-induced PARK6/Quinasa 1 (PINK1). Homozygous mutations in this gene were found originally in patients with early-onset Parkinson's, and account for between 1 to 2% of cases of early onset of Parkinson's disease (Hatano et al., 2004).

The PINK1 gene, located on 1p35-36, contains 8 exons spread over 1.8 kb and encodes a protein of 581 amino acids. The transcript is expressed ubiquitously and encodes a protein kinase domain of a highly conserved, which is also in the family of Ca^{2+} / calmodulin serine-threonine kinases (Valente et al., 2004).

DJ1 PARK7/Oncogen, DJ1 gene, located on chromosome region 1p36, contains 8 exons that span 24 Kb and is located 25 cM from the telomere of the PINK1 gene (Bonifati et al., 2003). Deletions have been identified and mutations that cause amino acid change <1% of early-onset parkinsonism (Lockhart et al., 2004).

Monogenic forms represent less than 10% of Parkinson disease in most populations and are the result of complex interactions between genes and environmental factors. Genetic variations could be susceptibility factors or disease modifiers, affecting the penetrance, age of onset, severity and progression.

The results of different studies show an association between Gaucher and Parkinson's disease by the occurrence of Gaucher disease and atypical parkinsonism in patients, appearing between the fourth and sixth decades of life, and the identification of mutations in the gene the *GBA* in probands with sporadic Parkinson's disease.

There are different hypotheses about how to explain the association of Parkinson disease and Gaucher Disease. One of them claims that glucocerebrosidase gene (*GBA*) mutations can produce an aberrant protein with function gain either hetero or homozygous and facilitate the alpha-synuclein aggregation this effect could induces neuronal toxicity. Wild-type alpha-synuclein could be selectively translocated into lysosomes for degradation by the chaperone-mediated autophagy pathway (Cuervo et al., 2004).

Under these conditions the receptor LAMP2 would saturate their transport capacity, resulting in a jam intracellular alpha-synuclein. Another scenario would involve directly the accumulation of misfolded mutated glucocerebrosidase protein in the endoplasmic reticulum leading to a situation of stress, and decreased activity of parkin, an ubiquitin ligase associated with the occurrence of early onset of Parkinson disease. This stress could trigger the start of the mechanisms of neuronal apoptosis in the substantia nigra, and therefore the onset of disease (Ron et al., 2010).

Moreover, only in patients with the two *GBA* mutant alleles the functional deficit of glucocerebrosidase, may cause accumulation of glucocerebroside and glucosphyngosine

that interfere with the determination of alpha-synuclein to lipid membranes, facilitating the aggregation of alpha-synuclein and the formation of Lewy bodies (Schlossmacher et al., 2005).

4.2 Other neurological manifestations in type 1 Gaucher Disease

Pastores et al conducted an epidemiological survey in order to ascertain the incidence of neurological symptoms in patients with GD1 (Pastores et al., 2003). This survey revealed that a significant proportion of patients with GD I experience neurological symptoms. In addition, we found that GD1 patients have a greater risk of suffering other common unrelated diseases than carriers or their healthy relatives (Giraldo et al., 2011). The wide spectrum phenotypic variation and neurological involvement within all types, and the recognition of an increasing number of subgroups of patients, support the view that GD is a disorder with a phenotypic continuum ranging from prenatal lethality to asymptomatic adults (Sidransky, 2004). Figure 2

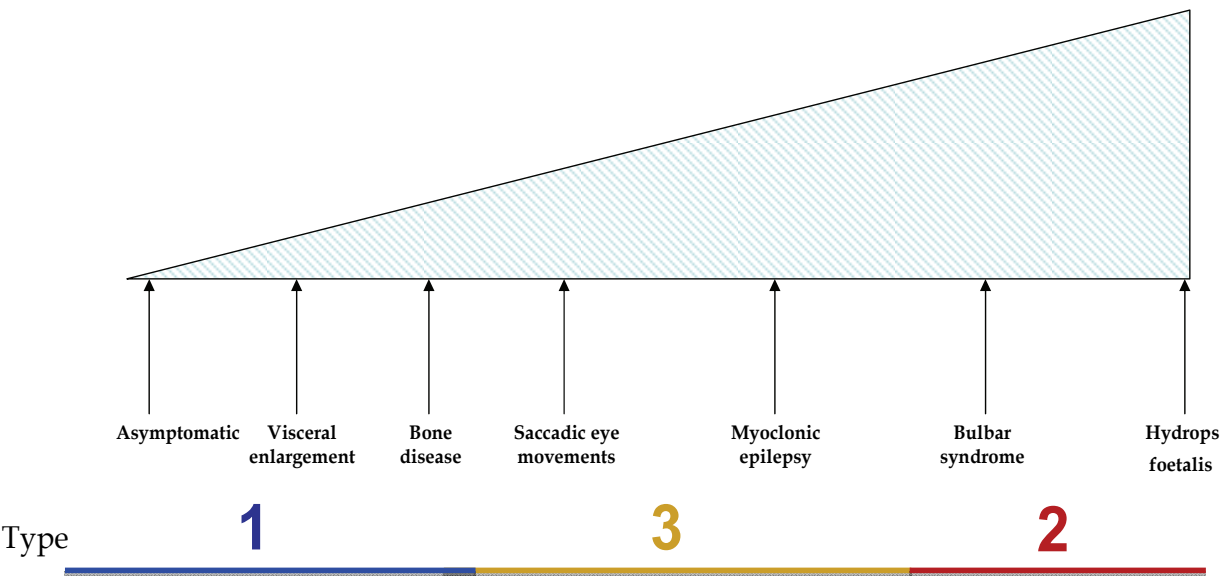


Fig. 2. Phenotype continuum in Gaucher disease

A recent systematic review of published literature identified 86 studies in which patients with GD1, or carriers of a glucocerebrosidase gene mutation, had some form of neurological manifestation (Biegstraaten et al., 2008; Cherin et al., 2010) contrary to the classical neuronopathic phenotypical description. Peripheral nervous system manifestations appear to be of particular relevance in GD1. An epidemiological survey of GD1 patients undergoing long-term enzyme replacement therapy (ERT) revealed that 73% of patients had at least one neurological symptom, including paraesthesia, tremor, muscular weakness, muscle cramps and sciatica, most of which were thought to be due to peripheral nervous system disease (Pastores et al., 2003). A case-control survey in 107 GD1 patients (untreated or receiving ERT) corroborated these findings, reporting a significantly higher frequency of symptoms related to peripheral neuropathy (Halperin et al., 2007). However, the above studies were limited by the absence of a neurological examination and standardised nerve conduction studies, and as yet there are no reliable estimates of the prevalence of peripheral neuropathy in GD1 (Biegstraaten et al., 2010), the vast majority of these cases have subclinical peripheral neuropathy only detected by electroneurophysiological exams. Figure 3

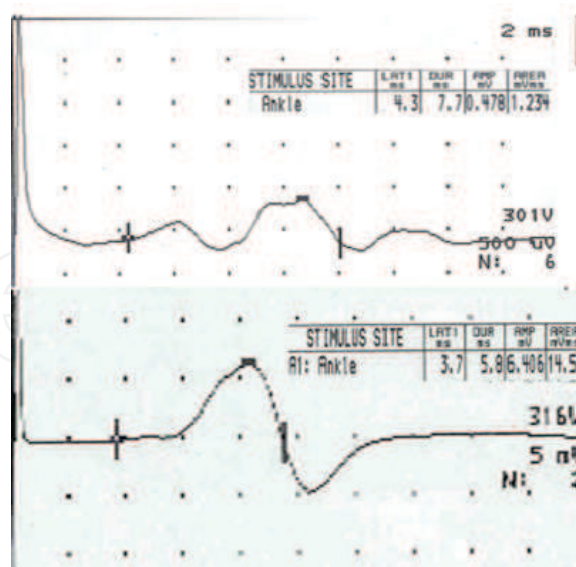


Fig. 3. Sensorial nerve conduction in type 1 Gaucher Disease patient. Abnormal wave forms in radial nerve.

The aetiology of polyneuropathy related to GD1 has not yet been elucidated, although certain associated conditions may predispose patients to develop neurological disease. Relevant conditions might include monoclonal gammopathies, vitamin B₁₂ deficiency and diabetes mellitus (Gielchinsky et al., 2001; de Frost et al., 2008; Silverman et al., 2008). The pathophysiology of nerve injury in GD remains speculative, but may be related to an imbalance in calcium homeostasis. Elevated intraneuronal glucocerebroside concentrations have been shown to induce a 300% increase in calcium-induced calcium release by influencing the RyaR channel, which has been proposed as one of the mechanisms responsible for neuronal injury in the central nervous system of neuronopathic GD (Lloyd-Evans et al., 2003). Whether this mechanism plays a role in peripheral nerve injury is unknown, but increased intracellular calcium has been implicated in the pathophysiology of diabetic neuropathy and neuropathic pain (Hall et al., 2001; Yaksh, 2006; Finnerup et al., 2007).

In conclusion, polyneuropathy and other peripheral nerve involvement appear to be part of the natural course of disease in patients with GD1, highlighting the need for increased vigilance for peripheral neurological abnormalities.

5. Mutations in *GBA* and neuronopathic forms of Gaucher Disease

The gene for human GCase, *GBA*, consists of 11 exons, have 7.2–7.4 kb in size, and maps to chromosome 1q21 (Barneveld et al., 1983). A pseudogene that shares 96% exonic sequence homology with *GBA* is located at 16 kb downstream from the functional gene (Horowitz et al., 1989). Figure 4. The pseudogene is transcribed, but does not produce a functional protein (Sorge et al., 1990). A significant number of mutations are present in the *GBA* pseudogene, and there are mutant alleles caused by gene conversion events with the pseudogene named recombinant alleles, Rec or pseudogene like mutations. Over 300 mutations have been identified worldwide in *GBA* and over 50 different mutations have been described in patients with neuronopathic involvement (Hruska et al., 2008) and also see

<http://www.hgmd.org>. They represent a spectrum of non-sense, missense and splice mutations as well as gene rearrangements. Most of these mutations are rare or private mutations, but two missense mutations, N370S and L444P, have significant frequencies in the majority of populations. It has been suggested that the genotype plays an important role in determining the degree of neurological involvement; however genotype-phenotype correlations are not straightforward in GD (Beutler & Grabowski., 2001; Koprivica et al., 2000). The most consistent finding is that the presence of the N370S mutation, either in homozygosity or in heterozygosity, always precludes development of neurological manifestation (Grabowski, 1997).

Chromosome 1q21

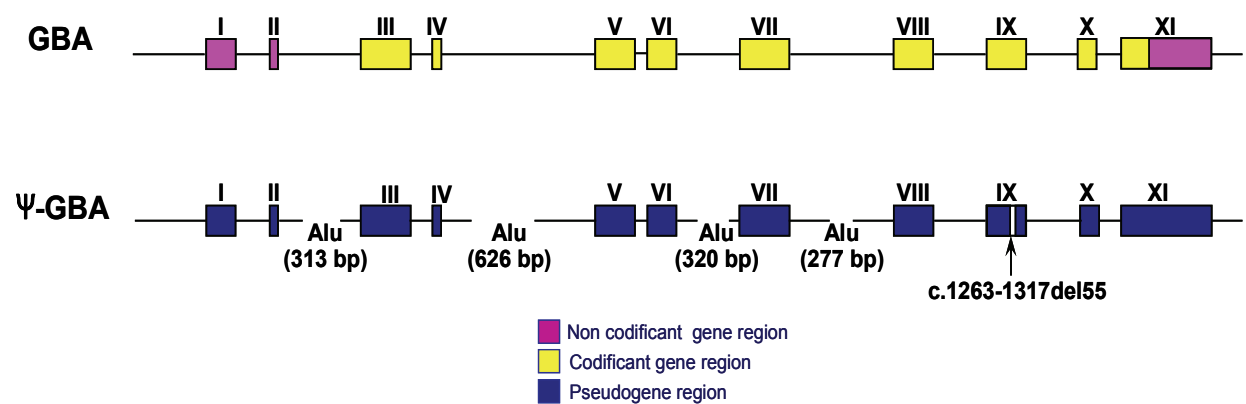


Fig. 4. Structure of glucocerebrosidase gene *GBA* and Seudogene Ψ -*GBA*

However, L444 P homozygosity has been shown to be associated with a neuronopathic phenotype in various populations, including Spanish, Swedish, Pole, Ashkenazi Jewish, and other Caucasian populations, while it was clearly associated with non-neuronopathic Gaucher disease in Taiwanese-Chinese (Wan et al., 2006; Goker-Alpan et al., 2005; Koprivica et al., 2000; Stone, 2000). These observations strongly suggest that other factors, such as modifier loci, promoter mutations, environmental factors, and other non-genetic causes, must play roles in the observed genotype-phenotype variability and also that modifying genes could be associated with the ethnic-related genetic diversity (Montfort et al., 2004; Alfonso et al., 2010).

To try to identify relationships genotype-phenotype, two approaches may be useful. First, the use of homogenous populations would tend to diminish genetic variation, as a consequence, the observed phenotype can be attributed to the identified mutants with greater assurance. However, this approach is limited by the need of large sample size to identify sufficient numbers of homozygotes for study, and to guarantee the homogeneity. The second approach is to study patients with most severe disease, and the least amount of residual activity. It is assumed that both mutant alleles have to be highly disruptive in these cases.

An additional problem arises from the analysis method used; most laboratories relied solely on Polymerase Chain Reaction (PCR) based mutation-detection techniques to screen for the presence or absence of specific mutations. PCR amplification of a specific fragment has

inherent problems, because a complex allele with more than one mutation, a mutation located at a primer site or a deleted allele could not be detected and therefore the published studies on genotype-phenotype relationship may be biased. Moreover, recombinant alleles would not be identified because using this approach alleles carrying a portion of the pseudogene sequence will not be amplified by primers designed to be specific for the glucocerebrosidase gene, and the patient may mistakenly be designated as a homozygote for the second allele (Torralba et al., 2002; Tayebi et al., 1999).

Given these limitations, we note that some generalizations were observed that suggested genotype-phenotype correlations: 1) homozygosis for the L444P mutation is usually, if not always, associated with neuronopathic forms 2). L444P is the most common mutation identified in patients with the intermediate phenotype. 3) the combination of one allele with L444P mutation and another mutation with a null or very severe allele seemed to be associated with the most severe neurological form, type 2. 4) perinatal lethality due to hydrops fetalis often resulted from homozygosis for a null or a recombinant allele. 5) None of the patients with type 2 are carriers of the N370S mutation, commonly found in GD1.

It is important to point out that there is an overlap between the GD2 and GD3 phenotypes making it difficult to categorize, on the other hand, the differentiation between GD1 and GD3 is sometimes difficult during early adulthood and the patients may have to be re-classified if neurological deficits, appear later in life. Therefore it is possible that Gaucher disease, classically divided into three types have a continuum of phenotypes.

There are a large number of genotypes associated with neuronopathic forms of GD. In Western countries, an association can be drawn between the presence of the N370S allele in combination with other mutation and GD1. Conversely, the L444P allele is most frequently associated to the neuronopathic variants. Data from 47 neurological cases included in the Spanish Gaucher Disease Registry, SGDR, (Alfonso et al., 2007; Giraldo et al., 2000) indicate that the most frequent allele is L444P accounting for 38.3% of the total alleles, followed by D409H 18.1% and the double mutant allele [E326K; L444P] 12.8%. Table 1.

Seventeen per cent of the total neurological GD cases included in the SGDR were homozygous for L444P mutation. It is interesting to note that this genotype was found in two patients classified as GD2 and in 6 GD3 and the homozygous for [E326K; L444P] as GD2. Surprisingly one patient with myoclonic epilepsy was carrier of N370S mutation, genotype N370S/G195W, no other mutations were identified in this patient in spite that the entire *GBA* was sequenced and analysed large rearrangements. It is important to point out that we do not know if in this case the cause of neurological impairment was due to the *GBA* gene or to other gene, gene-gene interaction or gene-environment interaction and therefore we dared not classify them as GD2 or GD3.

As we mentioned before the N370S mutation has been traditionally associated with the absence of neurological disease; however, several studies reported a high proportion of patients with the N370S mutation were diagnosed with GD 1 and showed mild neurological symptoms such tremor, peripheral neuropathy, uncoordinated movements, and hearing loss (as well as Parkinson disease. (Capablo et al., 2008; Giraldo et al., 2011; Pastores et al., 2003). These findings are consistent with the recently established contention that the mutation could not fully protect the patient from the appearance of neurological symptoms (Halperin et al., 2007). These observations reinforce the hypothesis that phenotypes reflect the continuum of the GD (Sidransky et al., 2004).

Genotype	Type2	Type3	Percent
L444P/L444P	2	6	17.0
D409H/D409H		6	12.8
[E326K;L444P]/R463H	3		6.3
G195E/L444P	3		6.3
c.1263_1317del55/L444P	3		6.3
D409H/R120W	2		4.2
D409H/L444P		2	4.2
[E326K;L444P]/[E326K;L444P]	2		4.2
[N188S;E326K]/L444P		2	4.2
R120W/L444P	2		4.2
[E326K;L444P]/D409H		1	2.1
[E326K;L444P]/P182L		1	2.1
[E326K;L444P]/G202R	1		2.1
[E326K;L444P]/W312R	1		2.1
[E326K;L444P]/L444P	1		2.1
G202R/L444P	1		2.1
I270P/L444P	1		2.1
RecNciI/L444P	1		2.1
S364R/L444P	1		2.1
c.203_204insC/L444P	1		2.1
G377S/G195W		1	2.1
R463C/G377S		1	2.1
N392I/L444P	1		2.1
V15M/G195W	1		2.1
Total	27	20	100

Table 1. *GBA* genotype distribution in 47 neuronopatic forms of GD from Spanish Gaucher Disease Registry

In a recent study, aimed to determine the presence of neurological symptoms and Parkinson’s disease in Spanish GD patients and their relatives, we have found that relatives with PD exhibited a wide spectrum of *GBA* mutations L444P, N370S, V398I, R257Q, G202R, c.1439- 1445del7, [E326K; N188S], and c.953delT in the other hand PD was more frequent in carriers of L444P mutation and other rare *GBA* mutations than carriers of N370S (Giraldo et al., 2011).

6. Treatment of neurological forms of Gaucher Disease

The standard care for GD patients is the enzymatic replacement therapy (ERT), unfortunately neurological manifestations of GD are not corrected by ERT. This failure should be attributed to the blood–brain barrier which is largely impermeable to proteins. It is noteworthy that children without neurological symptoms at diagnosis that receive early infusions of ERT, are bound to develop neurological symptoms in type 3 of disease. The other therapy approach used in glycosphingolipid disease, is the inhibition of the enzyme glucylceramide synthase and is called substrate reduction therapy (SRT), these inhibitors decrease the biosynthesis of the substrate (glucosylceramide). The only licensed

SRT is a small iminosugar molecule (Miglustat) that penetrates the blood-brain barrier. In spite of the trial conducted in children with chronic neuronopathic GD form, Miglustat do not meet its clinical end points and the drug currently is not recommended for neurological manifestations in GD. Nevertheless, there are some reports with specific neurological cases treated with miglustat that showed improvement in neurological manifestations (Capablo et al. 2007). It is interesting that miglustat used by compassionate therapy, in some type3 Gaucher disease gets to slow the progression of neurological manifestations, in similar manner that occurs in the licensed therapy with Miglustat in Niemann-Pick disease type C, another lysosomal disease that affects the brain in which there is disturbed cholesterol trafficking to lysosomes and causes secondary accumulation of glycosphingolipids in neurons (Wraith et al. 2010).

Bone marrow hematopoietic stem-cell transplantation, is not in current general use for GD, partly because of the difficulty to found ideal donors and procedural risks. The introduction of successful ERT has superseded this treatment in many countries. Only neurological forms in early stages could be rescued by this procedure.

The gene therapy is an interesting future option. The use of lentivirus-transduced autologous hematopoietic stem cells has been applied in other neurodegenerative disease as adrenoleukodystrophy (Cartier et al 2009) and currently in clinical trials for metachromatic leukodystrophy. Gene therapy has the advantage of being one procedure that requires less powerful myeloablative conditioning and thus is applicable for patients predicted to be at risk of severe neurological disease (Cox 2010).

7. Conclusions

Gaucher Disease is divided classically in three types based on the presence and rate of progression of the neurologic manifestations: type 1 non-neuronopathic, type 2 acute neuronopathic, and type 3 subacute neuronopathic. However there is an overlap between the different types suggesting that the disease have a continuum of phenotypes. There is accumulating evidence that in some Gaucher Disease patients classified as type 1, will develop neurological abnormalities during adult life such as peripheral neuropathy or early onset Parkinson Disease.

In spite of that, there are some glucocerebrosidase gene mutations associated more frequently to neurological forms, nevertheless genotype-phenotype correlations are not straightforward in Gaucher Disease.

The origin of neurological changes has not been clearly established, the neuropathological studies have demonstrated damage in several areas of the brain with perivascular Gaucher cells, astrogliosis and neuronal loss that could be attributed to intracellular deposits of glucocerebroside, and to abnormalities in calcium homeostasis.

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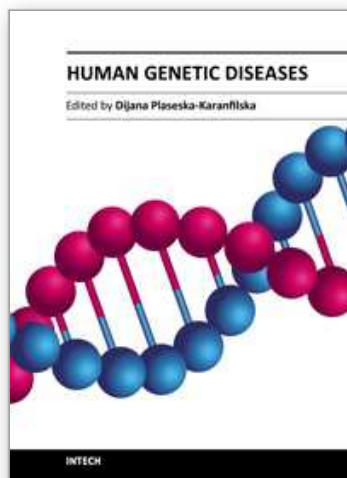
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The genetics science is less than 150 years old, but its accomplishments have been astonishing. Genetics has become an indispensable component of almost all research in modern biology and medicine. Human genetic variation is associated with many, if not all, human diseases and disabilities. Nowadays, studies investigating any biological process, from the molecular level to the population level, use the “genetic approach” to gain understanding of that process. This book contains many diverse chapters, dealing with human genetic diseases, methods to diagnose them, novel approaches to treat them and molecular approaches and concepts to understand them. Although this book does not give a comprehensive overview of human genetic diseases, I believe that the sixteen book chapters will be a valuable resource for researchers and students in different life and medical sciences.

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