

Gaucher's Disease and Hurler's Syndrome in Two First Cousins

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ABSTRACT Lysosomal storage diseases (LSD) are a group of approximately 50 autosomal recessive inborn errors of metabolism resulting from defects in lysosomal function. These diseases are progressive and multisystemic. The researchers' present two patients from Oaxaca, Mexico, and describe their findings from clinical evaluations, blood biometry, urinalysis, bone-marrow smears, X-rays, enzymatic measurements, and molecular studies. Patient 1, a 10-year-old school-age female with Gaucher's disease (sphingolipidosis) shows two previously unreported mutations in the glucosylceramide beta (GBA) gene. A homozygous mutation in exon 5 (c.463T>C; p.Tyr155His) and a heterozygous variant in exon 10 (c.1459C>A; p.Ala487Thr) were identified. Patient 2, a 3-year-old female suffering from Hurler's syndrome mucopolysaccharidosis type I due to a homozygous 12bp deletion from nucleotides 46 to 57 in the alpha-L-iduronidase (IDUA) gene. In summary, two first-degree Mexican patients with different forms of LSDs, and two previously unreported mutations in the GBA gene are described in this study.

INTRODUCTION

A heterogeneous group of glycoprotein acid-hydrolase enzymes are synthesized in the endoplasmic reticulum. These enzymes, such as the enzymes related to Lysosomal Storage Disorders (LSD), are then modified in the Golgi apparatus and packaged into vesicles or lysosomes (Ratko et al. 2013). LDS-related enzymes are associated with a range of conditions caused by inborn metabolic errors. LSDs are a result of reduced or null activity of lysosomal enzymes and an accumulation of a substrate within the lysosome. The resulting increased size of lysosomes interferes with normal cellular processes, although lysosomal diseases each have an incidence of between 1 in 5000 to 1 in 7000 in live

newborns (Gilbert 2007). LSDs are classified as sphingolipidosis (~5%), mucopolysaccharidosis (~34%), glycogenosis (~5%), and to a lesser extent, as mucopolipidosis, oligosaccharides, or lipofuscinosis (collectively ~6%). Classification of the disorders is determined by the nature of the defects at multiple levels: the degradation by lysosomal hydrolases, alterations of the synthesis and folding as well as defects in activation, substrates, and in membrane proteins. LSDs are inherited conditions characterized by a progressive and multisystemic disease. Many of them have an autosomal recessive mode of inheritance and may present mental retardation. These conditions manifest during childhood and no curative treatments are known. However, for some conditions, enzyme replacement therapy (ERT) is available (Desnick 2004).

Gaucher's Disease

Gaucher's disease (GD), the most frequent lysosomal storage disease, presents visceral and neurologic symptoms. Disruption of the catabolism of sphingolipids results in the accumulation of glucosylceramide (GlcCer) in lysosomes.

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This disruption is caused by a mutation in the acid-beta-glucocerebrosidase (Santos and Tiscornia 2017). GD has an incidence of 1 in 60,000 in the general population. Heterogeneous sphingolipidosis results from mutations in the glucosylceramide beta (GBA) gene that encodes the lysosomal enzyme, which hydrolyses glucosylceramide with a deposit in the mononuclear phagocytic cells. GD has three clinical subtypes: Type I is the adult (-non-neuropathic-) form, Type II is the infantile or acute neuropathic form, and Type III is the chronic neuropathic form. Since 1991, ERT has reduced the morbidity and mortality associated with GD. While GD Type I responds well to the treatment, GD Type II does not. Furthermore, the treatment response in patients with GD Type III is incomplete because there is no evidence of improved neurological function, but the treatment does attenuate the visceral or bone injuries associated with this clinical subtype (Carbajal et al. 2012).

GD Type I, or non-neuropathic, is the most common subtype affecting 1 in every 40,000 to 60,000 live newborns. It is caused by a homozygous mutation or a compound heterozygous mutation of the GBA gene (OMIM: 606463) on chromosome 1q22. The most common disease-causing (pathogenic) alleles are N370S (53%), L444P (18%), 84GG (7%), and IVS (2%) (Charrow et al. 2000). In Mexico, the most frequent clinical manifestations reported in affected patients are the following: anemia, asthenia, splenomegaly, hepatomegaly, bone crisis with episodes of fever and bone pain, spontaneous nose bleeds, gingival, petechia or ecchymosis, hypermenorrhea, fullness sensation, distension or abdominal pain, pale mucous and teguments, pathological fractures, and growth retardation (Franco-Ornelas 2010).

Mucopolysaccharidosis

Mucopolysaccharides (also known as glycosaminoglycans) are unbranched polysaccharide chains formed by repeating disaccharide units, which are synthesized by cells from the connective tissue. Degradation of these macromolecules occurs in lysosomes through a series of enzymes. A deficiency in any of these 11 enzymes, which are required for the degradation of dermatan sulfate, heparan sulfate, keratin sulfate, and chondroitin sulfate results in mucopolysaccharidosis (MPS) types I to VII. MPS

may be caused by the dysfunction in a single gene or a combination of genes. For example, MPS type IX is caused by a deficiency of hyaluronidase (Scriver et al. 2001).

Mucopolysaccharidosis I-Hurler's (MPS I-H) is caused by mutations in the IDUA gene encoding the lysosomal alpha-L-iduronidase enzyme. MPS I-H is a rare, deadly disease that affects 1 in every 100,000 live newborns (Parini et al. 2017).

Hurler/Scheie and Scheie syndromes are both caused by mutations in the IDUA gene; however, the milder phenotype associated with the Scheie's syndrome may be caused by residual enzymatic activity of the alpha-L-iduronidase (Jones 2013). An early age-of-onset is associated with the more severe MPS I-H, of which eighty percent of patients, in this spectrum, are classified, although there is a phenotypic overlap between these three syndromes (Pastores et al. 2007). In attenuated forms of MPS type I, the onset of symptoms starts at approximately 2 years of age, with an age of diagnosis at 15 months to 40 years of age. All types of MPS are autosomal recessive inherited with the exception of MPS type II (also known as Hunter syndrome), which has an X-linked recessive inheritance. Common clinical manifestations of MPS are joint contractures, corneal opacity, inguinal and/or umbilical hernia, carpal tunnel syndrome, cardiopathy/-valvular heart disease and dysostosis multiplex (Jones 2013).

METHODOLOGY

This clinical report describes two clinical patients: a 10-year-old female patient suffering from Gaucher's disease, and her first cousin, a 3-year-old female with Hurler's syndrome. Both come from a small community in the State of Oaxaca, Mexico. Detailed pedigree analysis, clinical and radiological evaluation, and blood biochemistry analysis were performed (from peripheral blood collected in a heparinized container). Enzymatic and molecular testing were performed by Centogene (SHIRE), the Lysosomal Diagnostic Laboratory at the Boston Children's Hospital (Sanofi-Genzyme) and Claritas Genomics.

RESULTS

Once medical records were compiled, a family tree was generated. The two patients are a

directly related being first cousins. Their family tree is depicted in Figure 1.

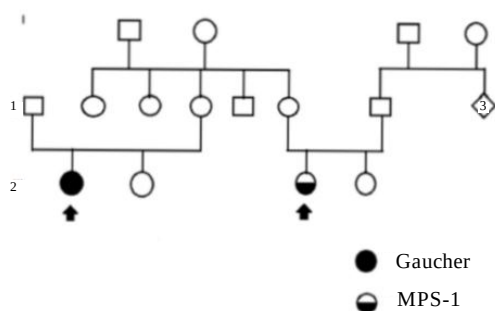


Fig. 1. Family tree showing both patients described in this study

Patient 1

For the 10-year-old female patient, in whom GD manifested in the first stages of life, frequent re-admissions to the hospital were necessary. During her last admission, the patient presented paleness, intense abdominal pain, arthralgias at knee level, and petechiae in the lower extremities. A physical examination was performed. She had a weight of 21kg, a height of 117cm (below 3rd percentile), and a body temperature of 37°C. Following examination of the thorax, she was identified as Normocephalic. She had isochoric pupils with normal reflection, an oral cavity with no alterations in the thorax, and a rhythmic heart beat with no other phenomena. Following an abdominal exam, an 8-8-6 splenomegaly below the costal margin was identified. This can be seen in Figure 2. Evaluation of the extremities



Fig. 2. Patient 1 with Gaucher's disease. Note protuberant abdomen caused by severe splenomegaly

determined scattered petechial injuries. The differential diagnoses, in addition to Gaucher's disease, in this patient were: leukemia, non-Hodgkin's lymphoma, and other lysosomal storage diseases.

The blood biometry showed that the patient was anemic, with a hemoglobin level of 10.7 gr/dL. The platelet count of 60,000 was compared to the normal reference range of 150,000-450,000. In addition, prothrombin and thromboplastin times (TP and TPT, respectively) showed increases when compared to reference values (shown in Table 1). Bone marrow aspiration revealed eight percent blasts, with no reported – Gaucher's cells.

The radiological assessment determined that the patient had severe splenomegaly and mild hepatomegaly, but no detectable ascites. X-ray imaging unveiled a thin calvaria of the skull (Fig. 3a), osteopenia in the femurs from Erlenmeyer flask deformity, and more generalized osteopenia (stage II) (Fig. 3b). These clinical findings match those of Gaucher's disease (Blass-Jaimes 2010) and Erlenmeyer flask deformity (Carter et al. 2012).



Fig. 3a



Fig. 3b

Fig. 3. Radiological findings of patient 1 with Gaucher's disease a) Microinfiltration with cortical changes in density in the skull b) Femurs with osteopenia and Erlenmeyer flask deformity

Table 1: Blood biometry of both patients in this study

<i>Parameter (unit)</i>	<i>Patient 1</i>	<i>Patient 2</i>	<i>Reference values**</i>
Hb (g/dL)	10.7	11.3	11.0-18.0
Hct (%)	32.7	36.7	35.0- 55
TP seconds	18.7	NM	14.5
TPT seconds	52.6	NM	34.0
Leukocyte x 10 ³ cells/mm ³	5260	16.1	4.5-10.0
Neutrophils (%)	2730	2.6-16	42.2-75.2
Lymphocytes (%)	NM	12.3-76.3	20-40
Platelets x. 10 ³ /mm ³	60,000	402,000	150,000-450 000

Prothrombin time (TP), Thromboplastin time (TPT), Hemoglobin (Hb), Hematocrit (Hct), Not measured (NM).

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Enzymatic and molecular testing established glucocerebrosidase and lyso-Gb1 concentrations of <3.5µmol/L/h and 671ng/mL respectively. Compared to reference values, the glucocerebrosidase activity was below the detection level (<0.8µmol/L/h), whereas that of the Lyso-Gb1 biomarker was considerably above the limit. Because of these findings, a molecular study of the GBA gene was performed and two novel mutations were identified. The first was a homozygous mutation (c.463T>C) predicting a substitution of an amino acid (aa) from tyrosine to histidine (p.Tyr155His). The second mutation was a heterozygous variant (c.1459G>A) with a predicted amino acid change from alanine to threonine (p.Ala487Thr). These predictions are shown in Table 2. Based on these findings, the patient was diagnosed with Gaucher's disease.

Patient 2

The second clinical case of the researchers' study was a female aged 2 years and 10 months. Her condition manifested from the first months of life, displaying frequent rhinorrhea with nasal obstruction, recurrent otitis media, corneal opacity, lower dorsal kyphosis, coarse facial features, and umbilical hernia. At 2 years and 11 months of age, she was transferred from the Health Center in San Baltazar Guelavila, Tlaxolula, located in the center of the state of Oaxaca, México, for a genetics consultation. Following her physical tests, she was found to be below the age-appropriate

weight and height. Her weight was 10.7kg, her height was 83cm which is below the 3rd percentile, and she had a head circumference of 47cm (25th percentile). Assessment of her facial features determined that she had coarse facial features with a wide and depressed nasal bridge, wide nostrils, thick lips, thick eyebrows, synophrys, and excessive facial hair. In addition, she presented corneal opacity, a wide and short thorax, rhythmic heart-beat, and no other phenomena. Examination of the abdomen identified an umbilical hernia of approximately 4cm, and a liver of 5cm below the costal margin. Examination of the thorax identified that the patient had hyperlordosis with a low dorsal hump, large dermal melanocytosis and normal female external genitalia (Fig. 4a, b, c).

Blood biometry testing described normal values with the exception of a high total Leukocyte white blood cell count of 16.08 (Table 1). The results of urinalysis were normal, and liver function tests established a total protein content of 7.0ng/mL and an alkaline phosphatase content of 211ng/mL, which exceeds the reference range of 38-126ng/mL.

In the extremities, she was diagnosed to have difficulties with joint extension and had mild camptodactyly in both hands. Using X-ray imaging a bony thorax with lumbar hyperlordosis and ovoid-shaped vertebral bodies were identified (Figs. 5a, b). In addition, the hands had short and wide tubular bones with a bullet-shaped base (Fig. 5c).

Table 2: Molecular analysis of the GBA gene in patient 1

<i>Location</i>	<i>Nucleotide change</i>	<i>aa change</i>	<i>Reference</i>	<i>Classification</i>
Exon 5	c.463 T>C (homozygous)	p.Tyr155His	Cento MD	Disease-causing
Exon10	c.1459 G>A (heterozygous)	p.Ala487Thr	None	Likely to be disease-causing



Fig. 4a



Fig. 4b



Fig. 4c

Fig. 4. Patient 2 with Hurler's syndrome presenting a) Coarse facial features, wide, depressed nasal bridge, wide nostrils, thick lips, and thick eyebrows b) Large dermal melanocytosis/Mongolian spots (excessive) and c) Umbilical hernia



Fig. 5a



Fig. 5b



Fig. 5c

Fig. 5. Radiological features of patient 2 with Hurler's syndrome. Assessment of the thorax identified a) Kyphosis and a thoracolumbar hump in addition with b) Ovoid-shaped vertebral bodies c) The hands had short, -wide, bullet-shaped, and tubular bones

Enzymatic and molecular tests measured an IDUA concentration of $0.19 \mu\text{mol/L/h}$. In addition, the molecular analysis showed a homozygous mutation in the IDUA gene of patient 2 (Sanofi-Genzyme). The variant was a 12bp dele-

Table 3: Molecular analysis of the IDUA gene in patient 2

<i>Classification</i>	<i>Zygosity</i>	<i>Nucleotide-change</i>	<i>aa change</i>	<i>dbSNP ID</i>
Pathogenic	Homozygous	c.46_57delTCGCTCCTGGCC	p Ser16_Ala19del	rs398123260

tion from nucleotides 46 to 57 that resulted in a predicted amino acid loss of Serine 16 to Alanine 19. Based on these findings, the patient was diagnosed with Hurler's syndrome (MPS type IH).

DISCUSSION

A significant challenge for epidemiological studies of LSDs is based on the significant clinical heterogeneity found in these conditions. This results in diagnostic uncertainty and missed diagnoses, both of which are reflected in weak epidemiological data, leading to an underestimation of the impact of LSDs in the community (Fuller et al. 2006).

Although LSDs can appear in any human population, their prevalence may differ (Meikle et al. 1999). Furthermore, while the severe phenotypes of these diseases can be diagnosed at an early age, attenuated or less severe forms may present challenges in their diagnosis.

As found in previous studies of isolated communities such as the Ashkenazi Jewish and Finnish populations, inbreeding in isolated populations increases the prevalence of autosomal recessive diseases (Fuller et al. 2006). In this study, both cases occur in San Baltazar Guelavila, a town located in the Municipality of San Dionisio Ocotepec, Tlaxolula, in the state of Oaxaca in Mexico. The town has 3130 inhabitants and the predominant indigenous group is Zapotec. From approximately the year of 1529, crossbreeding began in this region of Oaxaca (INEGI 2000) with a prevalence of genic mutations found in this small and inbreeding population. This prevalence may be accounted for by differences in immigration patterns or isolation, for instance, because of geographical, lingual, ethnic or religious preferences (Kingma et al. 2015).

Although clinical presentation of LSDs is dependent on the clinical signs and symptoms, there are a number of overlapping features that are not specific to these conditions. The most prominent indications and symptoms for correct diagnosis and identification of LSDs are the

loss of previously acquired cognitive and motor skill, with or without additional signs or symptoms affecting different organs or organ systems (Wilcox 2004).

Over 200 mutations of the GBA gene have been identified in patients with Gaucher's disease (OMIM 606463).

The researchers' found that the first patient described here had an extremely high concentration of lyso-Gb1 (671 -ng/mL) compared to a reference value of ≤ 4.8 ng/mL, whereas her level of glucocerebrosidase (< 3.5 μ mol/L/h) was below the reference value of ≥ 4.9 μ mol/L/h.

Molecular analysis identified two previously unreported mutations in the GBA. One was a homozygous mutation in exon 5 (c.463T>C; p.Tyr155His) that was located in a moderately conserved nucleotide and a highly conserved amino acid position. Moderate physicochemical differences between tyrosine and histidine were predicted at this location. Analyses using Polyphen-2, SIFT, Mutation Taster and Align-GVGD showed that the variant was "probably damaging." The second mutation was a heterozygous variant in exon 10 (c.1459G>A, p. Ala 487 Thr) this was located in a highly conserved nucleotide and amino acid position with a predicted small physicochemical difference between the amino acids alanine and threonine. Our data is available in the Centogene database.

The second patient, who was diagnosed with Hurler's syndrome (also known as mucopolysaccharidosis type I, showed a homozygous deletion of 12bp46-57delTCGCTCCTGGCC (p.Ser16-Ala19del). This mutation, which has been previously reported (<http://snpedia.com/index.php/Rs398123260>, and 141_IDUA_V1.pdf), is known to cause Hurler's syndrome when present in either the homozygous or compound heterozygous state (Bunge et al. 1994; Bertola et al. 2011).

Functional studies have demonstrated that homozygous individuals with this deletion have little to no residual enzyme activity. Different populations, including Italian, Turkish, Polish, Mexican and Chinese have been associated with Hurler, Hurler-Scheie and Scheie phenotypes (Kingma et al. 2015). In the patient suffering from Hurler's disease the researchers' measured an

IDUA concentration of 0.19 $\mu\text{mol/L/h}$. This indicates an absence of these enzymes in comparison to the reference value of $\geq 2 \mu\text{mol/L/h}$.

In addition, and according to the protocol of Claritas Genomics (info@claritasgenomics.com), two homozygous benign sequence variants, which have not been previously reported, were identified. In these instances, the researchers believe that homozygosity of sequence variants is more likely at these positions. However, other less likely explanations include: 1) a shared common ancestor or haplotype, 2) deletion of one of the alleles, 3) uniparental disomy (UPD), or 4) allele dropout because of a rare sequence variant(s), which interferes with primer binding. To identify one of these four possibilities, multiplex ligation-dependent probe amplification (MLPA) testing can detect exonic deletions but is not definitive in determining UPD or shared ancestry.

Among other approaches, ERT has advanced in clinical practice and represents a beneficial strategy for 8 out of the 50-60 known LDs (Solomon and Muro 2017). In the recent years, significant progress has been made in the treatment of lysosomal diseases. This advancement is remarkable as, until now, only symptomatic treatments were accessible. ERT is available in both GD and Hurler syndromes. ERT in patients with GD reduces many of the systematic manifestations caused by the disease and prevents its complications from progressing (Pastores et al. 2004; Vijay and Wraith 2005; Muenzer et al. 2009; Cox 2010). In patients with Hurler's disease, ERT improves the range of body articulation. In prepubertal patients, treatment results in substantial growth and preservation of myocardial function (Sifuentes et al. 2007). However, the enzyme does not cross the blood-brain barrier, and therefore, does not prevent the mental retardation found in patients with Hurler's syndrome. Prognosis depends on the age of diagnosis, the degree of organ involvement, and the individual's response to treatment.

Gaucher's disease affects between 1200 and 1500 Mexicans, although just twenty percent of the cases are diagnosed, and of these, only ten percent are treated (Diagnostico y tratamiento de Enfermedad de Gaucher Tipo I. Mexico: Secretaria de Salud. 2011. www.cenetec.salud.gob.mx) In Mexico, the incidence of Hurler's disease is estimated at 1 in every 100,000 live newborns, although the exact number of affected individu-

als is not known. Enzymatic treatment is being provided to patients as well as counseling for their parents.

The patient diagnosed with Gaucher's disease has already started ERT with velaglucerase- α , VPRIV (®) (Shire Human Genetic Therapies) at the "Hospital del Niño Poblano" in San Andrés Cholula in Puebla, México. A recommended dosage of 60 units/kg body weight is being administered every two weeks. The patient diagnosed with Hurler's syndrome has already started ERT, using, laronidase (Aldurazyme®) from Genzyme, also at the Hospital del Niño Poblano. The recommended dosage is 100 units (0.58mg) per kg body weight in a continuous intra-venous perfusion once a week.

The challenge for patients and families is to deal with life threatening and chronic diseases, which generate continuous stress. The study of rare diseases is increasing owing to their clinical importance to the population. However, the lack of empirical data in the field, which would enable development of better policies and strategies to treat this population, provides the need for further research (Somanadhan and Larkin 2016).

CONCLUSION

Confirmation of two first-cousins with LSD is reported, one suffers from Gaucher's disease (sphingolipidosis) and the other patient from Hurler's diseases (mucopolysaccharidosis).

RECOMMENDATIONS

Primary care providers and pediatricians must be aware of the signs and symptoms of these disorders in order to pursue early diagnosis. Therefore, the surveillance by the medical team is essential. The disadvantages of both diseases are that treatments are for life. Nevertheless, in Mexico, progress to legalize the administration of these therapies is being made, taking into account individualized ethical considerations in each case. The eventual strategy towards providing and informing patients about ERT will be determined by a multi-disciplinary group at a recognized center for referrals. All the diagnostics and treatments need to follow the protocols established by the referral centers in order to provide a basis for evaluating the clinical data obtained to make comparisons and define the best treatment.

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