Int J Hum Genet, 17(3): 109-117 (2017)
DOI:10.31901/24566330.2017/17.03.03

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

**Patricia Fenton-Navarro[1*], Eduardo Pérez-Campos[2, 3], María del Socorro Pina-Canseco[2] and Bertha Fenton-Navarro[4]**

*[1*]Genetics Department, "Dr. Aurelio Valdivieso" General Hospital, Oaxaca, Oax Health Services Oaxaca, Mexico*
*[2]Research Center, Faculty of Medicine, UABJO-UNAM, Oaxaca, México*
*[3]Department of Biochemistry and Immunology, ITO-UNAM, Oaxaca, Mexico*
*[4]Glycobiology Laboratory, Postgraduate Studies Division, Faculty of Medicine and Biological Sciences "Dr. Ignacio Chávez", UMSNH, Morelia, México*
*[*]E-mail: patricia.fenton.n@gmail.com*

**KEYWORDS** Lysosomal Storage Diseases. MPS Type IH. Sphingolipidosis. Gaucher. Inbreeding

**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 mucolipidosis, 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).

*Address for correspondence:*
Dr. Patricia Fenton Navarro
Genetics Department,
"Dr. Aurelio Valdivieso" General Hospital,
Oaxaca, Oax Health Services,
Porfirio Díaz # 400 Colonia Reforma,
Oaxaca, Oax México CP 68050.
*Telephone/Fax:* (52)9515044135, (52)9515201667
*E-mail:* patricia.fenton.n@gmail.com

### 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.

This disruption is caused by a mutation in the acid-beta-glucocerebroside (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 alfa-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 alfa-L-iduronidase (Jones 2013). An early age-of-onset is associated with the more severe MPS 1-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.

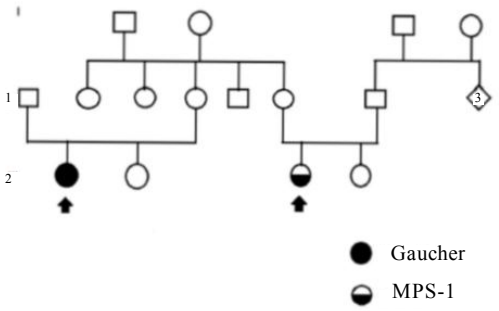


**Fig. 1. Family tree showing both patients described in this study**

## 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 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.

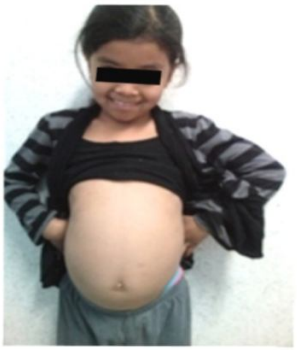

**Fig. 2. Patient 1 with Gaucher's disease. Note protuberant abdomen caused by severe splenomegaly**

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).

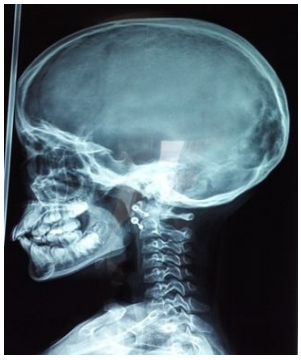

**Fig. 3a**

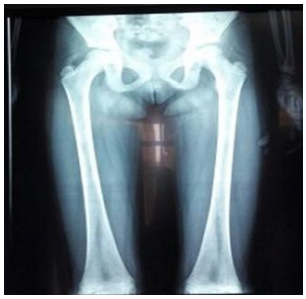

**Fig. 3b**

**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**

| *Parameter (unit)* | *Patient 1* | *Patient 2* | *Reference values*** |
|---|---|---|---|
| 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).
** The Central Laboratory of the "Dr. Aurelio Valdivieso" General Hospital, Oaxaca, Oax, México.

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, Tlacolula, 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 Leucocyte 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**

| *Location* | *Nucleotide change* | *aa change* | *Reference* | *Classification* |
|---|---|---|---|---|
| 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 |

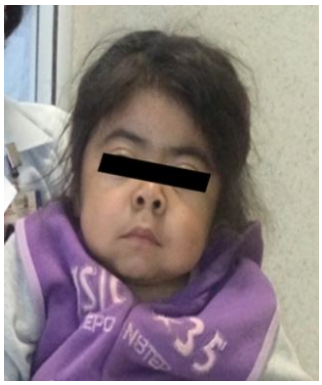

Fig. 4a

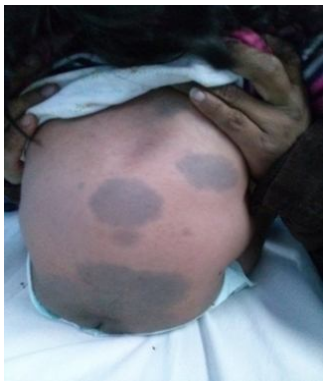

Fig. 4b

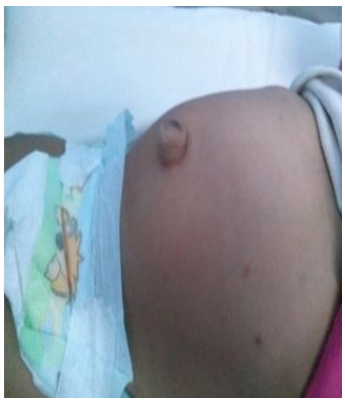

Fig. 4c

**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**

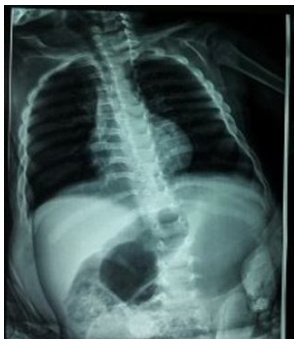

Fig. 5a

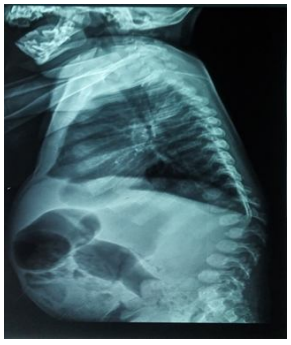

Fig. 5b

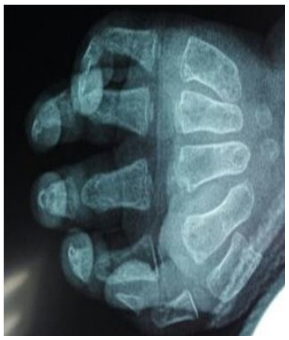

Fig. 5c

**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 0.19µmol/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**

| *Classification* | *Zygosity* | *Nucleotide-change* | *aa change* | *dbSNP ID* |
|---|---|---|---|---|
| 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, Tlacolula, 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 $\leq$4.8ng/mL, whereas her level of glucocerebrosidase (<3.5µmol/L/h) was below the reference value of $\geq$4.9µmol/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 0.19μmol/L/h. This indicates an absence of these enzymes in comparison to the reference value of ≥2μmol/L/h.

In addition, and according to the protocol of Claritas Genomics (info@claritas genomics.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 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 Enfermeded 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 individuals 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 -alfa, 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.

## ACKNOWLEDGEMENTS

The researchers thank the patients and their families for participating in this study. They extend their appreciation to Centogene (SHIRE) Order no: 62226216 for the genetic and molecular analysis of patient 1, and to the Lysosomal Diagnostic Laboratory at the Boston Children's Hospital (Sanofi-Genzyme) and to Claritas Genomics (CLIA # 15-08721BIDU) for the enzyme and molecular investigation of patient #2.

The researchers thank the chemists, Vicente Cruz Méndez, Edith Toledo López, and Mónica Herrera Hurtado for sample acquisition and Dr. Elvira Silvet Chiñas López for elaborating on the Family tree.

The researchers also thank the Pediatric Service, Hematology, Hematology-Oncology, Radiology, Clinical Laboratory, and Seguro Popular for the support given to patients and their families, and the Hospital del Niño Poblano and its staff for starting infusion treatment for both patients.

## REFERENCES

Bertola F, Filocamo M, Casati G, Mort M, Rosano C, Tylki-Szymanska A, Tüysüz B, Gabrielli O, Grossi S, Scarpa M, Parenti G, Antuzzi D, Dalmau J, Di Rocco M, Dionisi Vici C, Okur I, Rosell J, Rovelli A, Furlan F, Rigoldi M, Biondi A, Cooper DN, Parini R 2011. IDUA mutational profiling of a cohort of 102 European patients with mucopolysaccharidosis type I: Identification and characterization of 35 novel alpha-L-iduronidase (IDUA) alleles. *Human Mutation,* 32: E2189-E2210.

Blass-Jaimes P 2010. Manifestaciones óseas en enfermedad de Gaucher's entre pacientes mexicanos. *Acta Ortopédica Mexicana,* 24: 351-358.

Bunge S, Kleijer WJ, Steglich C, Beck M, Zuther C 1994. Mucopolysaccharidosis type I: Identification of 8 novel mutations and determination of the frequency of the two common alpha-L-iduronidase mutations (W402X and Q70X) among European patients. *Hum Mol Genet,* 3: 861-866.

Carbajal L, Gómez F, Rodríguez R, Zarco J, Mora-Tiscareño M 2012. Terapia de reemplazo enzimático en una paciente con enfermedad de Gaucher'stipo III. *Acta Pediatr Mex,* 33: 9-19.

Carter A, Rajan PS, Deegan P, Cox TM, Bearcroft P 2012. Quantifying the Erlenmeyer flask deformity. *The British Institute of Radiology,* 85: 905-909.

Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, Pastores G, Rosenbloom BE, Scott CR, Wappner RS, Weinreb NJ, Zimran A 2000. The Gaucher's registry: Demographics and disease characteristics of 1698 patients with Gaucher's disease. *Arch Intern Med,* 60: 2835-2843.

Cox TM 2010. Gaucher's disease: Clinical profile and therapeutic developments. *Biologics,* 4: 299-313.

Desnick RJ 2004. Enzyme replacement and enhancement therapies for lysosomal diseases. *J Inherit Metabol Dis,* 27: 385-410.

Franco-Ornelas S 2010. Consejo Mexicano de Enfermedad de Gaucher. *Rev Med Inst Mex Seguro Soc,* 48: 167-186.

Fuller M, Meikle PJ, Hopwood JJ 2006. Epidemiology of lysosomal storage diseases: An overview. In: A Mehta, M Beck, G Sunder-Plassmann (Eds): *Fabry Disease: Perspectives from 5 Years of FOS.* Oxford: Oxford Pharma Genesis, P. 16.

Gilbert BE 2007. Metabolic diseases. In: E Gilbert, RP Kapur, LL Oligny, JR Siebert (Eds.): *Potter's Pathology of the Fetus, Infant and Child.* 2nd Edition. Philadelphia: Mosby Elsevier, pp. 463-572.

Jones KL 2013. Mucopolysaccharidosis I H, IH/S, I S. In: *Smith's Recognizable Patterns of Human Malformation*. USA: Saunders Company, pp. 596-597.

Kingma SDK, Bodamer OA, Frits A, Wijburg FA 2015. Epidemiology and diagnosis of lysosomal storage disorders: Challenges of screening. *Best Pract Res Clin Endocrinol Metab,* 29: 145-157.

Meikle PJ, Hopwood JJ, Clague AE, Carey WF 1999. Prevalence of lysosomal storage disorders. *JAMA,* 281: 249-254.

Muenzer J, Wraith JE, Clark LA 2009. Mucopolysaccharidosis I: Management and treatment guidelines. *Pediatrics,* 123: 19-29.

Parini R, Deodato F, Di Rocco M, Lanino E, Locatelli F, Messina C, Rovelli A, Scarpa M 2017. Open issues in Mucopolysaccharidosis type I - Hurler's. *Orphanet J Rare Dis,* 12: 112-120.

Pastores GM, Weinreb NJ, Aerts H, Andria G, Cox TM, Giralt M, Grabowski GA, Mistry PK, Tylki-Szymañska A 2004. Therapeutic goals in the treatment of Gaucher's disease. *Semin Hematol,* 41: 4-14.

Pastores GM, Arn P, Beck M, Clarke JT, Guffon N, Kaplan P, Muenzer J, Norato DY, Shapiro E, Thomas J, Viskochil D, Wraith JE 2007. The MPS I registry: Design, methodology, and early findings of a global disease registry for monitoring patients with Mucopolysaccharidosis Type I. *Mol Genet Metab,* 91: 37-47.

Ratko TA, Marbella A, Godfrey S, Aronson N 2013. Enzyme-Replacement Therapies for Lysosomal Storage Diseases Technical Brief. No. 12. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-2007-10058-I.) Rockville, MD: Agency for Healthcare Research and Quality. From <http://www.effectivehealthcare.ahrq.gov/ehc/products/364/1368/TB12_ Enzyme Replacement Therapies_FinalReport_20130102.pdf>.

Santos D, Tiscornia G 2017. Induced pluripotent stem cell modeling of Gaucher's disease: What we have learned? *J Mol Sci,* 18: 888.

Scriver RC, Beaudet LA, Sly WS, Valle D, Child B et al. 2001. The Mucopolysaccharidosis. In: *The Metabolic and Molecular Bases of Inherited Disease.* Volume III. USA: McGraw-Hill, pp. 3421-3668.

Sifuentes M, Doroshow R, Hoft R, Mason G, Walot I, Diament M, Okazaki S, Huff K, Cox GF, Swiedler SJ, Kakkis ED 2007. A follow-up study of MPS I patients treated with Iaronidase enzyme therapy for 6

years. *Molecular Genetics and Metabolism,* 90: 171-180.

Solomon M, Muro S 2017. Lysosomal enzyme replacement therapies: Historical development, clinical outcomes, and future perspectives. *Adv Drug Deliv Rev*, (In Press).

Somanadhan S, Larkin PJ 2016. Parents' experiences of living with, and caring for children, adolescents and young adults with Mucopolysaccharidosis (MPS). *Orphanet J Rare Dis,* 11: 138-152.

Vijay S, Wraith JE 2005. Clinical presentation and follow-up of patients with the attenuated phenotype of mucopolysaccharidosis type 1. *Acta Paediatr,* 94: 872-877.

Wilcox WR 2004. Lysosomal storage disorders: The need for better pediatric recognition and comprehensive care. *J Pediatr,* 144: S3-S14.

**Paper received for publication on March 2017**
**Paper accepted for publication on August 2017**