

Received: 2018.09.12  
Accepted: 2019.02.06  
Published: 2019.05.14

# A 42-Year-Old Woman with Untreated Growth Hormone Insensitivity, Diabetic Retinopathy, and Gene Sequencing Identifies a Variant of Laron Syndrome

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**Conflict of interest:** None declared  
**Source of support:** This study was supported by the Fundación de Investigación HM Hospitales and Tecnológico de Monterrey

**Patient:** Female, 42  
**Final Diagnosis:** Never-treated growth hormone insensitivity due to IGF-1 deprivation  
**Symptoms:** Cataracts • mammary underdevelopment • severe hearing loss  
**Medication:** —  
**Clinical Procedure:** Early detection of IGF-1 deprivation and urgent consensus for current diagnosis  
**Specialty:** Endocrinology and Metabolic





**Objective:** Rare co-existence of disease or pathology  
**Background:** Growth hormone insensitivity and reduced levels of insulin-like growth factor-1 (IGF-1) are associated with metabolic syndrome that includes obesity, hyperglycemia, type 2 diabetes mellitus, and dyslipidemia. Laron syndrome is a rare autosomal recessive condition associated with insensitivity to growth hormone that results in short stature and metabolic syndrome and is usually diagnosed in childhood. This report is of a 42-year-old Mexican woman with untreated growth hormone insensitivity and diabetic retinopathy, in whom gene sequencing supported the identification of a variant of Laron syndrome.

**Case Report:** A 42-year-old Mexican woman with untreated growth hormone insensitivity, metabolic syndrome, and type 2 diabetes mellitus was diagnosed with cataracts, severe retinopathy and hearing loss. She was investigated for genetic causes of reduction in IGF-1. Next-generation sequencing (NGS) showed genetic changes in the growth hormone and IGF-1 axis. The patient's phenotype and genetic changes were consistent with Laron syndrome.

**Conclusions:** The early detection of reduced IGF-1 and identification of the cause of growth hormone insensitivity require international consensus on the approach to diagnosis and treatment methods, including effective IGF-1 replacement therapy. Early diagnosis may reduce the clinical consequences of complications that include short stature the development of metabolic syndrome, type 2 diabetes mellitus, and retinopathy.

**MeSH Keywords:** Diabetic Retinopathy • Insulin-Like Growth Factor I • Laron Syndrome • Metabolic Syndrome X

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/913178>

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## Background

In 1966, Laron and colleagues first described Laron syndrome, which is associated with dwarfism and is due to growth hormone resistance [1]. Laron syndrome is a hereditary autosomal recessive disorder caused by changes in the growth hormone receptor (*GHR*) gene [2]. The condition of growth hormone insensitivity is a broader concept that also covers several syndromes associated with conditions that affect post-receptor signaling molecules, associated receptor turnover regulator proteins [2], or *GHR* gene pseudoexon activation [3]. These phenotypic variants of growth hormone resistance are usually associated with a milder phenotype than that originally described by Laron [4]. Other syndromes, such as 3-M (Miller, McKusick, and Malvaux) syndrome and Russell-Silver syndrome (RSS), may have overlapping phenotypes that include growth retardation and skeletal abnormalities, possibly because of shared defects that affect insulin-like growth factor 1 (IGF-1) generation or signaling pathways. Reduced IGF-1 synthesis by the liver explains the low circulating levels of IGF-1 and the high or normal serum levels of growth hormone in children with syndromes associated with growth hormone resistance, including dwarfism, dysmorphic features and metabolic syndrome [5–7].

The metabolic impact of a chronic reduction in IGF-1, starting in utero, directly and indirectly affects carbohydrate metabolism [7].

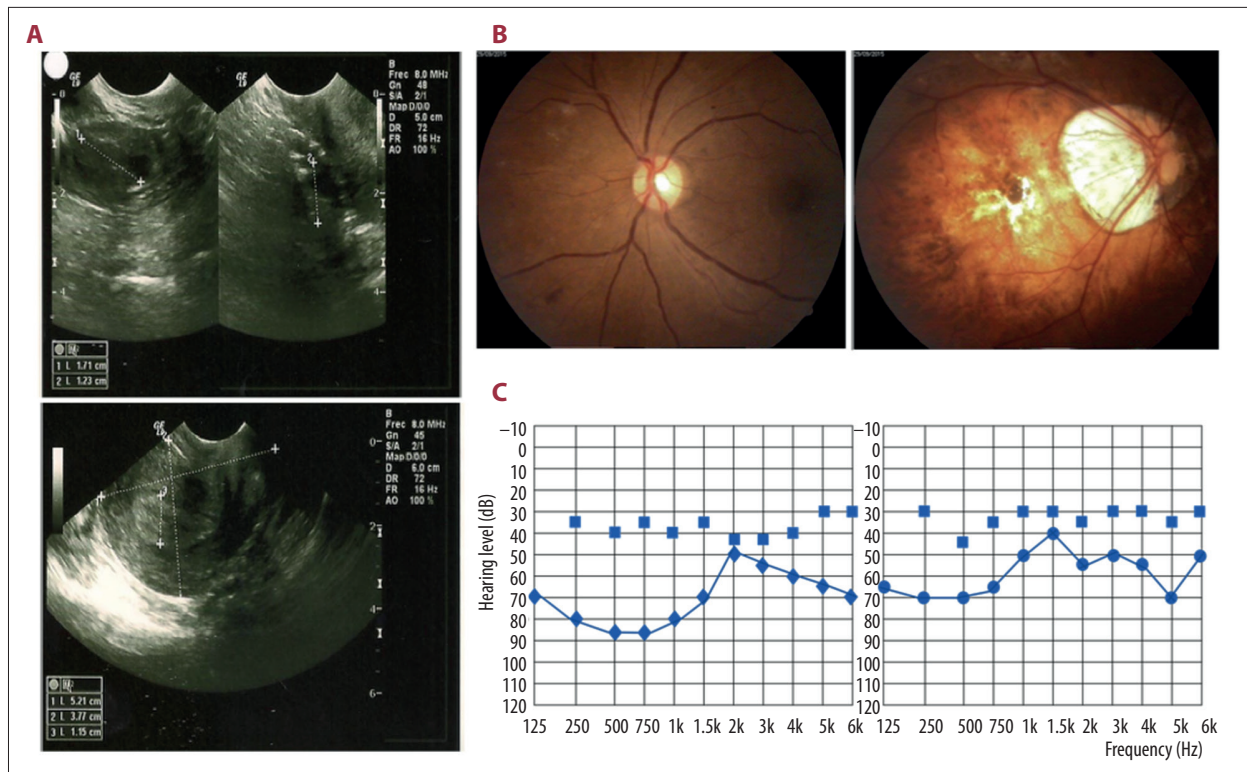
The symptoms of obesity and compensatory mechanisms for hypoglycemia affect sex hormones, and glucocorticoids [1,5,8–10]. Growth hormone insensitivity results in dynamic changes in carbohydrate and lipid metabolism in patients with untreated Laron syndrome or growth hormone insensitivity, which can be life-threatening when of long duration. Investigations into the mechanisms of growth hormone insensitivity may identify new pathways in the metabolism and regulation of growth hormone. During early childhood, patients present with hypoglycemia and then progressively develop hyperinsulinemia followed by hypoinsulinemia, glucose intolerance, and around puberty, type 2 diabetes mellitus, and hyperlipidemia develop [7,11]. Therefore, patients with untreated Laron syndrome or growth hormone insensitivity develop metabolic syndrome and type 2 diabetes mellitus in adulthood [7,11].

There are different opinions regarding the metabolic abnormalities in untreated patients with Laron syndrome or growth hormone insensitivity [12]. The findings from a recent study in mice with partial IGF-1 deficiency showed reduced hepatic expression of genes coding for glucose metabolism (*G6GC*, *PCK1*, *PDK4*, and *ACLY*) and lipid metabolism (*ACCA1B*, *ACAT1*, *HMGCS1*, *HMGRC*, *PCSK9*, *LRP1*), but IGF-1 replacement therapy did not normalize the genetic profile [13].

This report is of a 42-year-old Mexican woman with untreated growth hormone insensitivity and diabetic retinopathy, in whom



**Figure 1.** Physical examination of a 42-year-old woman shows hip dysplasia, abdominal obesity, and some of the phenotypic features of Laron syndrome (height, 124 cm and weight, 40 kg).



**Figure 2.** Pelvic transabdominal ultrasound, funduscopy and retinal examination, and pure-tone audiometry findings in a 42-year-old woman with a variant of Laron syndrome. **(A)** Pelvic transabdominal ultrasound. Upper panel: the right and left ovaries measure 1.5×1.0 cm and 1.0×0.7 cm, respectively. There are sparse antral follicles. Lower panel: anteflexed uterus measures 5.2×3.7 cm and a progestational endometrium of 11 mm. **(B)** Funduscopy of the retina. Left panel: the retina of the left eye shows diabetic retinopathy with hemorrhages and hard exudates. Right panel: the retina of the right eye shows macular and peripapillary retinal atrophy, choroidal neovascularization, and microhemorrhages secondary to severe myopia. **(C)** Pure-tone audiometry. **Left panel:** the left ear shows severe mixed hearing loss. **Right panel:** the right ear shows moderate to severe mixed hearing loss. The square dots represent bone conduction. The diamond (left ear) and the circle (right ear) correspond to air conduction.

gene sequencing supported the identification of a variant of Laron syndrome.

## Case Report

### Recent presentation and findings on examination

A 42-year-old Mexican woman was referred to our department after a previous diagnosis of Laron syndrome was made based on the appearance of dwarfism. The patient had a high-pitched voice. Physical examination showed hypoplasia of the nasal bridge, increased visceral fat, and hip dysplasia (Figure 1) [14,15]. At the time of presentation, she was 124 cm in height, and weighed 40 kg, with a body mass index (BMI) of 25.6 kg/m<sup>2</sup> (Figure 1). Her blood pressure was 123/81 mmHg, her heart rate was 75 bpm, with a respiratory rate of 18 breaths/min, and oxygen saturation of 98%. Symmetrical pulses were present in the lower extremities and she had ischemia of the feet due to peripheral vascular disease as a complication of type 2 diabetes mellitus.

### Past medical history

The patient was the seventh of ten children from a non-consanguineous Mexican marriage. The patient reported a family history of type 2 diabetes mellitus, nephropathy, hypertension, and cancer. Her paternal grandfather died from pancreatic cancer and was of short stature. She was born preterm and was hospitalized for three weeks after birth. She had an inability to walk and sit until she was 9 years old, possibly due to hip dysplasia (Figure 1). At the age of 14 years, she became morbidly obese, with a weight of 80 kg over adult weight, which required medical treatment. She was diagnosed with type 2 diabetes mellitus at the age of 23 years and was initially treated with glibenclamide and metformin. A year later, she began to be treated with insulin. Arterial hypertension was also diagnosed, which was initially treated with chlorthalidone and then captopril, due to the side effects of chlorthalidone. The patient was married with no offspring. She reported menarche at 9 years of age with menstrual cycles every 20 days with four days of normal menstrual bleeding. She denied the use of any method

**Table 1.** Hematology results in a 42-year-old woman with a variant of Laron syndrome.

Hematology test results		
Parameter	Value	Reference range
Leucocytes	9.6×10 <sup>3</sup> /μl	4.5–11.0
Erythrocytes	4.6×10 <sup>6</sup> /μl	4.2–5.8
Hemoglobin	12.8 gr/dl	12.6–16.6
Hematocrit	39.2%	36.6–52.4
MCV	85.0 fl	82.0–98.0
MCHb	27.6 pg	27.0–31.0
MCHC	32.5%	32.0–36.0
RDW	13.9%	11.7–15.5
Platelets	420×10 <sup>3</sup> /μl	150–420
Lymphocytes	28.8%	20.0–40.0
Monocytes	6.5%	3.3–13.3
Eosinophil	2.4%	1.0–5.0
Basophils	0.8%	0.0–1.0
Neutrophils	61.5%	50.0–70.0
Neutrophils*	5.9×10 <sup>3</sup> /μl	2.5–7.0
Lymphocytes*	2.8×10 <sup>3</sup> /μl	1.0–4.0
Monocytes	0.6×10 <sup>3</sup> /μl	0.2–1.2
Eosinophils*	0.2×10 <sup>3</sup> /μl	0.0–0.5
Basophils*	0.1×10 <sup>3</sup> /μl	0.0–1.0

MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; MCV – mean corpuscular volume; RDW – red cell distribution width. \* Represents the number of blood cell components.

of family planning, dysmenorrhea, and had no screening mammography. The date of her last menstrual period was reported 42 days before the date of hospital referral. The findings from gynecological examination showed mammary underdevelopment but without other abnormalities. Her external genitalia was of normal appearance for her chronological age, and examination of the internal genitalia showed a normal cervix. Transabdominal pelvic ultrasound showed very small ovaries and an anteverted uterus (Figure 2A).

#### Laboratory investigations on hospital admission

Blood chemistry showed an increased blood glucose level (254 mg/dl), increased blood urea nitrogen (BUN) (38 mg/dl), and glycosylated hemoglobin (HbA1c) (10.7%) (Tables 1, 2). A normal hemoglobin level and a normal hematocrit excluded anemia. There was a low serum insulin-like growth factor-1

**Table 2.** Biochemistry results in a 42-year-old woman with a variant of Laron syndrome.

Biochemistry test results		
Parameter	Value	Reference range
Blood glucose	<b>254 mg/dl*</b>	60–100
Creatinine	0.9 mg/dl	0.6–1.1
Blood urea nitrogen (BUN)	<b>38 mg/dl*</b>	7–20
Uric acid	5.9 mg/dl	2.6–6.0
Glycosylated hemoglobin (HbA1c)	<b>10.70%*</b>	4.27–6.07

\* Abnormal result.

**Table 3.** Urinalysis results in a 42-year-old woman with a variant of Laron syndrome.

Urinalysis		
Parameter	Value	Reference range
Appearance	<b>Cloudy*</b>	Clear
Colour	Straw-colored	Yellow-amber
Urinary density	<b>1.018*</b>	1.005–1.030
pH	6.0	4.6–8.0
Proteins	<b>0.03 g/dl*</b>	0
Glucose	<b>&gt;1000 mg/dl*</b>	0
Cetones	0 mg/dl	0
Bilirubin	0 mg/dl	0
Hemoglobin	Traces	Negative
Nitrites	Negative	Negative
Urobilinogen	Normal U/Erich	Negative
Urine microscopy		
Erythrocytes	3–4/μl	0–2
Leucocytes	21–22/μl	0–2
Epithelial cells	Few	Few
Mucus	Negative	Few
Crystals	Few amorphous	Few
Cylinders	Negative	Negative
Bacteria	A lot	Few
Yeast	Negative	Negative

\* Abnormal result.

(IGF-1) of 60 ng/ml (normal age-corrected range, 97–263 ng/ml) and a very low insulin-like growth factor-binding protein 3 (IGFBP-3) level of 1.9 mg/l (normal age-corrected range,

**Table 4.** Genetic changes in the growth hormone and insulin-like growth factor-1 (IGF-1) axis in a 42-year-old woman with a variant of Laron syndrome.

Gene	<i>GHR</i>	<i>NOD2</i>	<i>NFKB1</i>
Variant	A>A/C	C>C/T	T>T/TA
Chr	5	16	4
Coordinate	42719239	50745926	103534740
Type	snv	snv	Insertion
Genotype	het	het	het
Transcript	NM_001242399.2	NM_022162.1	
Consequence	Missense variant	Missense variant	Splice region variant, intron variant, feature elongation
Protein Position	551	702	
Amino Acids	I/L	R/W	
Codons	ATC/CTC	CGG/TGG	
Sift		Deleterious (0)	
PolyPhen		Possibly damaging (0.846)	
dbSNP ID	rs6180	rs2066844	rs148268461, rs34021443

*GHR* – growth hormone receptor; *NOD2* – nucleotide-binding oligomerization domain-containing protein 2; *NFKB1* – nuclear factor kappa B subunit 1; snv – single nucleotide variant; het – heterozygous.

3.3–6.7 mg/l) were found, together with low basal growth hormone levels (0.09 ng/ml) and no clonidine stimulation response. Urinalysis showed a cloudy appearance with increased glucose levels (>1000 mg/dl), as a result of hyperglycemia, and proteinuria (0.03 g/l) (Table 3).

#### Visual and auditory investigations on hospital admission

Visual acuity testing showed impaired vision and included corrected visual acuity test (right eye 20/400, left eye 20/30), refraction of the right eye –18.50 and left eye (–0.75 and –1.50 at 100). Quadrant field testing showed anterior segments with cortical cataracts in three right-eye quadrants and in the left eye lens with cortical cataract in four left-eye quadrants. Fundal examination (Figure 2B) showed a scleral crescent, retinal atrophy, and choroidal neovascularization in the right eye, associated with high myopia. In the left eye, intraretinal hemorrhage and hard exudates were found as signs of diabetic retinopathy. Ocular dimensions of the right eye included a longitudinal axial of 28.94 mm, an anterior chamber depth of 3.14 mm, and a lens thickness of 4.18 mm. Ocular dimensions of the left eye included a longitudinal axial of 22.89 mm, an anterior chamber depth of 3.14 mm, and lens thickness 4.26 mm. Also, audiometry showed severe mixed hearing loss in both ears (Figure 2C).

#### Gene profiling using next-generation sequencing (NGS)

Molecular diagnosis used next-generation sequencing (NGS) using a TruSight One Kit (Illumina, San Diego, CA, USA) in a MiSeq Sequencer (Illumina, San Diego, CA, USA). Gene changes were identified in genes involved in the growth hormone and IGF-1 axis (Table 4). Two heterozygous exon missense single nucleotide variants (SNPs) were identified, one in the *GHR* gene (dbSNP, rs6180 variant, A>A/C; chromosome 5, coordinate 42719239), and the *NOD2/CARD15* gene (dbSNP, rs2066844; variant, C>C/T; chromosome 16, coordinate 50745926). Sift (deletion 0) and polymorphism phenotyping (PolyPhen) (0.846) algorithms for the *NOD2* gene predicted an altered protein product.

The ClinVar Database ([www.ncbi.nlm.nih.gov/clinvar/](http://www.ncbi.nlm.nih.gov/clinvar/)) identified several reports for the mutation in *NOD2*, which was cataloged as of uncertain pathogenic significance. An important insertion was also found in the *NFKB1* gene splice donor site (dbSNP, rs148268461, rs34021443; variant, T>T/TA; chromosome, 4; coordinate, 103534740), which has been previously reported in sequencing projects, but with unknown clinical significance. No variants or mutations were found that could explain a deficiency in growth hormone. Importantly, no family segregation analysis could be performed as both parents were deceased. This patient is no longer alive.

## Discussion

Worldwide, the estimated incidence of Laron syndrome is approximately 1–9 per million, and between 250–500 cases have been reported [16,17]. However, if growth hormone insensitivity is taken into consideration the number of cases increases, but the exact prevalence remains to be determined [6,16]. Cases tend to be unreported, particularly those arising from areas of scarce medical recourses, such as in Mexico and other Latin American countries, where dwarfism may be considered to be common and does not cause concern for an association with morbidity. Poor access to necessary tests and the costs of testing using growth hormone stimulation tests and molecular diagnosis limit the diagnosis. In Mexico, the use of treatments using growth hormones are banned and the high cost of recombinant human insulin-like growth factor-1 (IGF-1) treatment all prevent more cases from being diagnosed and reported. Laron has also recently highlighted that without hope of treatment, children with Laron syndrome will continue to be undiagnosed [17].

Laron syndrome has been mainly reported in consanguineous families in the Mediterranean, Middle Eastern, or South Asian countries, and there is a large reported population found in El Oro, Ecuador [18]. In our experience, Laron syndrome, or growth hormone insensitivity and IGF-1 deficiency, is a more common condition in Mexico. Unfortunately, the natural history of untreated patients with Laron syndrome or growth hormone insensitivity and the association with metabolic syndrome, obesity, and type 2 diabetes and serious complications, including death, remain poorly understood [14,19]. The patient in this report developed metabolic abnormalities, which developed into impaired vision, uncontrolled blood glucose levels, and hearing loss, and the patient has early mortality. In addition to being crucial in growth and pubertal development, IGF-1 is a key regulator of bone and cartilage formation, and deficiency has been linked to osteopenia and bone abnormalities [14,19–21]. Therefore, deficiency of IGF-1 explains the finding of congenital hip dysplasia and delayed ability to stand and walk (Figure 1). Also, IGF-1 is critical for normal intrauterine development, and deficiency has recently been reported to be associated with fetal growth restriction [22]. As the patient presented in this report was born preterm, this finding may have also supported the diagnosis of congenital IGF-1 deficiency at an earlier stage.

Despite her young age, the patient in this report suffered from severe diabetic retinopathy due to type 2 diabetes mellitus that developed early in life, and has been reported in untreated patients with growth hormone insensitivity [12,23]. Retinopathy as a consequence of chronic reduction on IGF-1 levels is not usual in the progression of obesity-induced type 2 diabetes mellitus and diabetic retinopathy. In addition to dwarfism, patients with untreated growth hormone insensitivity also

develop obesity and type 2 diabetes mellitus, and both are also features of chronic IGF-1 deficiency, as shown in this patient [10]. Also, reduced levels of IGF-1 could explain the symptom of hearing loss, as this hormone plays a crucial role in the development of the inner ear [24–27].

The missense polymorphism found in the *GHR* gene is present in the population with a mean allele frequency of 0.5, according to the Exome Aggregation Consortium (ExAC) that includes 1000 genomes ([www.exac.broadinstitute.org](http://www.exac.broadinstitute.org)). However, the clinical relevance of the prevalence of the missense polymorphism found in the *GHR* gene remains unknown. Therefore, in this case, the analysis of compound oligogenic changes instead of Mendelian monogenic mutations was performed, and the findings indicated that the downregulation of the growth hormone and IGF-1 axis resulted in growth hormone insensitivity. The first mutation identified is an important insertion found in the *NFKB1* gene, which encodes for nuclear factor kappa B subunit 1 (NF-KB1). This crucial transcription factor is the most potent activator of signal transducer and activator of transcription 5B (STAT5B) and phosphoinositide 3-kinases (PI3K) synthesis [28], the former being the receptor substrate and transcription factor for the generation of IGF-1 and insulin-like growth factor-binding protein 3 (IGFBP-3) by the liver, and the latter being important in the *GHR* gene activation pathway [28,29]. Also, NF-KB1 is activated by IGF-1 receptor and *GHR* gene signaling [28], and PI3K-Akt ultimately activates *NF-KB1*. Therefore, growth hormone insensitivity may result as both growth hormone and IGF-1 resistance arise from low expression of the *GHR* and *IGF1R* genes due to the *NF-KB1* variant, and because IGF-1 may not be fully produced due to the same variant. This same effect, in terms of growth hormone and IGF-1 resistance, was previously reported in a patient bearing a mutation in the *IKBA* gene (a *NF-KB1* suppressor) [30]. Also, the missense polymorphism found in the *NOD2/CARD15* gene may increase the severity of the growth hormone insensitivity phenotype, as patients with this mutation have previously been reported to develop hepatic growth hormone insensitivity, linear growth failure, Crohn's disease, and antibodies against granulocyte-macrophage colony stimulating factor (GM-CSF) [31].

In the patient presented in this case, IGF-1 deficiency was associated with low basal growth hormone and no response to clonidine. This finding may result in diagnostic confusion, as growth hormone deficiency is characterized by the inadequate secretion of growth hormone from the pituitary gland, resulting in reduced IGF-1 levels. Growth hormone insensitivity or resistance is the consequence of several changes in the *GHR* gene signaling pathway that result in IGF-1 deficiency. The difference between these disorders is that patients with primary deficiency of growth hormone have pituitary dwarfism with a typical phenotype of a large skull, short stature, and

shortened extremities. However, patients with growth hormone insensitivity have a primary IGF-1 deficiency that causes short stature with proportioned head and limbs (Laron's dwarfism), a high-pitched voiced, hip dysplasia, and a tendency to metabolic disorders [19]. Some patients with growth hormone insensitivity have a limited and short-term response to the exogenous administration of growth hormone. It is clear that the most effective treatment for these patients is with IGF-1 replacement therapy, as they are deficient in this hormone.

In the patient presented in this report, there was no molecular genetic explanation for the low growth hormone levels found. In the present case, the untreated and chronic low levels of IGF-1 resulted in metabolic syndrome and type 2 diabetes mellitus, and other metabolic changes, that established the predisposition to reduced growth hormone levels. In our experience, it is common to find a depletion curve for growth hormone after stimulation with clonidine in adult patients with untreated chronic IGF-1 deficiency. This finding has been assumed to be due to a hypophysis and pituitary exhaustion response, in a mechanism similar to that of beta-cell exhaustion and ultimate cessation insulin production in type 2 diabetes mellitus, or may often be a false-negative in routine testing. Also, reduced levels of IGF-1 due to growth hormone insensitivity could remove the negative feedback mechanism required for the regulation of growth hormone, as IGF-1 is known to negatively regulate growth hormone via somatostatin in the adrenal cortex [32]. All these reasons demonstrate the importance and urgency to effectively diagnose and treat patients with growth hormone insensitivity from the early stages to avoid complications resulting from reduced IGF-1 levels and the development of a long-term increase in growth hormone later in life, and the associated patient morbidity and mortality.

## Conclusions

This case report of a 42-year-old Mexican woman with untreated growth hormone insensitivity and diabetic retinopathy included gene sequencing that supported the identification of a variant of Laron syndrome. This case demonstrated a phenotype that included a combination of hip dislocation,

retinopathy, short stature, voice changes, hearing loss, reduced insulin-like growth factor-1 (IGF-1) levels, pubertal obesity leading to adult metabolic syndrome, and type 2 diabetes mellitus, which supported a diagnosis of growth hormone insensitivity. The genetic causes of growth hormone insensitivity remain unknown, but developments in gene sequencing techniques have begun to identify the genetic causes of IGF-1 deficiency and growth hormone insensitivity that have a milder adult phenotype than classical Laron syndrome. Although there have been only a few hundred cases of Laron syndrome, or growth hormone insensitivity, reported worldwide [17], the prevalence may be much higher, particularly in certain populations, including the Mexican population. This case and its findings support the views recently made by Laron [17], that there is an urgent need to develop a consensus for the diagnosis and treatment of IGF-1 deficiency to prevent the long-term complications, including premature death.

## Acknowledgments

The authors thank Dr Zvi Laron and the medical teams of the Departments of Ophthalmology, Gynaecology, Pediatrics, Endocrinology, and Internal Medicine of Hospital Zambrano-Hellion (San Pedro Garza García, NL, México) and the Clinical Laboratory of Hospital San José, Monterrey, México. The authors also thank Dr. Mario Villegas (Centro de Audición y Equilibrio de Monterrey), Irene Martín del Estal and Karl Steinmetz.

## Ethical approval and patient consent

This case report was approved by Tecnológico de Monterrey Ethics Committee (protocol code: PREVLAR).

## Institution where work was done

Tecnológico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey, NL, Mexico

## Competing interests

None.

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