Importance of Long-Term Follow-Up in the Prognosis of Mucopolysaccharidosis IV-A: A Case Report from Southwestern of Colombia

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Abstract

Mucopolysaccharidosis IV-A (MPS IV-A) is an autosomal recessive genetic disorder caused by a deficiency in the enzyme N-acetylgalactosamine-6-sulfatase, leading to the accumulation of chondroitin-6-sulfate (C6S) and keratan sulfate (KS). This is a rare disease, and, in Colombia, it is classified as an orphan disease under Resolution 023 of 2023. Notably, its incidence in Colombia is higher than that reported in other countries worldwide. Genomic analysis of the GALNS gene has identified more than 400 variants in affected individuals, enabling genotype-phenotype correlations. We report the case of a patient who was initially presented at the age of 5 with short stature, lower limb dysmetria, and genu valgum. Physical examination revealed coarse facial features, a short neck, pectus carinatum, multiple joint deformities, and ligamentous hyperlaxity. Enzymatic activity of GALNS was reported at 0.06 mmol/mL/hour, and complete sequencing of the GALNS gene was performed using next-generation sequencing (NGS) technology, identifying the homozygous variant c.239C>T (p.Ser80Leu), which is associated with MPS IV-A. A bioinformatic analysis classified this variant as pathogenic. This case underscores the importance of clinical presentation, the use of diagnostic methodologies, and confirmation through molecular and bioinformatic studies for an accurate and timely diagnosis, as well as the critical value of appropriate clinical follow-up.

Keywords:

Lysosomal Storage Diseases, Phenotype**,** Genotype, Bioinformatics, Mucopolysaccharidosis IV (*DeCS*).

Introduction

Mucopolysaccharidosis IV-A (MPS IV-A or Morquio Syndrome IV-A) (OMIM #253000; Orpha 582) is classified as a lysosomal storage disorder (LSD) with an autosomal recessive inheritance pattern. It is caused by pathogenic variants in the GALNS gene, located on chromosome 16q24.3 [1]. The enzyme N-acetylgalactosamine-6-sulfatase (EC 3.1.6.4) is a 120 kDa homodimer comprising two functional domains [2], and it is expressed in 27 different tissues, including the cardiovascular, digestive, immune, integumentary, nervous, respiratory, skeletal muscle, and urinary systems—with predominant expression in skeletal muscle, testes, and lungs [3]. This disorder is characterized by a deficiency in GALNS enzymatic activity, resulting in the progressive accumulation of glycosaminoglycans (GAGs), particularly chondroitin-6-sulfate (C6S) and keratan sulfate (KS), which are key components of proteoglycans found in cartilage and bone [4]. Genomic analyses of GALNS across diverse

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ethnic populations have identified over 400 variants, enabling genotype-phenotype correlations in affected individuals [5].

MPS IVA is a low-frequency disorder, with an estimated frequency of 1 in every 75,000 to 1 in every 200,000 births worldwide and an approximate prevalence of 1 in every 250,000 live births. It is considered the most common mucopolysaccharidosis in Colombia, with an approximate prevalence of 1 in every 201,000 live births [3]. Recent studies on the epidemiology of MPS IV-A in our country show that it has the highest proportion of positive cases at 58.4% of all types of MPS, in addition to having an incidence rate of 3/100,000 live births [6], which is notably high compared to other countries such as the United States with 0.11/100,000 live births [7], Sweden with 0.07/100,000, Norway with 0.76/100,000 live births, Denmark with 0.48/100,000 live births, all considering types A and B [8], and Taiwan with 0.33/100,000 live births [9]. The high incidence of MPS IV-A in Colombia may be attributed to the fact that most patients exhibit a severe and readily recognizable phenotype [6]. This disorder is included in the most recent Resolution 023 of 2023 on orphan diseases in Colombia, under ICD-10 code E76.2. According to data from SIVIGILA, a total of 58 cases of MPS IV were reported in 2019. In comparison, the national report on orphan and rare disease events documented a total of 6,657 cases of orphan-rare diseases in 2022, with only 7 cases corresponding to MPS IV reported up to the sixth epidemiological week of that year.

The clinical presentation of the disease is very heterogeneous, which can pose a significant challenge for early recognition. The main manifestations of MPS IV-A are at the musculoskeletal level and connective tissues, causing various clinical manifestations that progressively evolve and affect quality of life; however, it can affect any other system except the central nervous system. Some of these include short stature, bone deformity, ligamentous hyperlaxity, and structural abnormalities in the thorax and spinal cord, recurrent infections and airway obstruction, Recurrent hernias are common, along with more severe manifestations such as visceromegaly, valvular heart disease, and various sensory impairments [3].

The diagnosis of this syndrome begins with clinical suspicion, radiographic imaging studies, and biochemical analysis of the deficient enzyme in leukocytes or fibroblasts in peripheral blood, with this being the confirmatory test. However, to determine the severity of the condition and expand the understanding of variants that cause the disease, molecular and genetic techniques allow for genotype-phenotype correlation and provide accurate genetic counseling [4]. Regarding treatment, specific therapeutic approaches such as enzyme replacement therapy (ERT), allogeneic hematopoietic cell transplantation, substrate degradation enzyme therapy, gene therapy, and other proposals like nanomedicine and chaperone therapy are currently available [10].

In general, MPS is diagnosed late or incorrectly over prolonged periods of time and affected patients must see many specialists before receiving a specific diagnosis, which negatively impacts the course of their disease [6]. Based on this, the aim is to highlight the importance of early recognition, as this is a key point for timely TRE implementation and to avoid serious complications, to emphasize the role of genetic tools for variant identification and bioinformatics tools for clinical prediction for genotype-phenotype correlation, proper genetic counseling, to provide individualized care, and to seek the approach of 6P medicine (personalized, predictive, preventive, participatory, population-based, and precision), in addition to ensuring optimal follow-up for patients with the disease. In this study we describe the long-term follow-up of a patient with MPS IV-A.

Clinical Case

16-year and 9-month-old female patient, product of the second pregnancy of non-consanguineous parents, with no history of exposure to toxins or teratogens. Born vaginally at 38 weeks of gestation after a threat of preterm labor at 34 weeks with induction of pulmonary maturity, without complications, with anthropometric measurements of weight 2,700 grams and height 47 cm, neonatal adaptation index Apgar 9-10-10 and without any pathology requiring hospitalization. Important family history includes a father with hypoglycemia and on the maternal side, a grandfather with hypertension who had a cerebrovascular accident, as well as his great-grandmother. There is no history of bone dysplasias or other genetic diseases.

Initial nutrition was based on breastfeeding for the first 15 months, alternating with formula feeding, and the introduction of complementary foods occurred at one year of age. Neurodevelopment was normal, with developmental milestones achieved within expected timeframes. Growth parameters remained within -1 to +1 standard deviations until the age of 5, when growth retardation became evident, with a height of 94 cm. At that age, signs of lower limb dysmetria were observed, predominantly on the left side, along with muscular atrophy, genu valgum affecting gait, a short neck, and facial swelling. Subsequently, hand joint deformities developed, including a claw-like posture and ligamentous hyperlaxity. Based on these clinical manifestations and the suspicion of Mucopolysaccharidosis type IV-A (MPS IV-A), a GALNS enzyme activity assay was performed at age 6, revealing a value of 0.06 mmol/mL/hour (reference range: 2–35.9), which confirmed the diagnosis.

At age 7, cervical spinal cord compression was identified, necessitating surgical intervention, and enzyme replacement therapy (ERT) with elosulfase alfa (Vimizim) was initiated via weekly intravenous infusions. At age 10, surgical correction of lower limb and knee deformities was performed. At age 13, the patient experienced menarche, and myopia was diagnosed, more pronounced in the right eye, requiring corrective lenses. At age 14, removal of osteosynthesis material from the lower limbs was carried out, and an allergic reaction to chicken consumption—associated with ERT—was documented, along with partial dental enamel loss.

Starting from the diagnosis of MPS IV-A and with the aim of performing the genotype-phenotype correlation, providing targeted care, timely follow-up, and genetic counseling, in 2022, complete sequencing of the GALNS gene (16q24.3) was

requested using NGS technology from a peripheral blood sample and using the GRCh37 genome as a reference, identifying the homozygous missense variant c.239C>T (p.Ser80Leu) located in exon 2/14. Finally, one year later, deformity in the upper limbs was reported with distal and proximal radioulnar dislocation and joint instability, in addition to heavy and prolonged menstrual bleeding, which is why low-dose oral estrogens combined with progestins were initiated every 24 hours.

Currently, upon physical examination, the patient presents anthropometric measurements of height 102 cm and weight 26 kg for a BMI of 24.9, abdominal circumference 69 cm, thoracic circumference 70 cm, wingspan 109 cm, length of the right third finger 13.5 cm, length of the left third finger 13 cm, length of the right lower limb 61 cm, and length of the left lower limb 59 cm. Upon inspection, there is a Trendelenburg gait, a swollen face, bushy eyebrows with synophrys, a wide and depressed nasal bridge, low-set ears, a short neck, and a scar from cervical spinal cord compression surgery, pectus carinatum, a globose abdomen without the presence of organomegaly, joint malformations with multiple dysostosis, claw hands, ligamentous hyperlaxity, genu valgum, and asymmetric short stature, without cognitive deficit.

The follow-up conducted on the patient shows mild deformity of the lumbar vertebrae L1-L2, osteopenia, and scoliosis with left convexity, a shortening of 4 mm in the total length of the left lower limb (LL), genu valgum of the knees, widened proximal metaphysis of the tibia, and flattened metaphysis of the tibia and femur, decreased bone density, and metatarsals with proximal angle, hypertrophy of adenoids, and spirometry showing a mixed component with greater restrictive involvement. Additionally, good adherence to the TRE weekly dose (2 mg/kg/week) is documented, along with a notable decrease in the concentration of quantitative urinary GAGs. Cardiac, renal, hepatic, and thyroid function is preserved, and there are no signs of visceromegaly or new bone complications (Table 1). The

Table 1. Follow-up conducted on the patient with MPS IV-A

FOLLOW-UP				
Evaluation	Tests	Date	Result	
Musculoskeletal	X-ray of dorsal lumbar spine	02/03/2020	Mild deformity in the lumbar vertebral bodies L1-L2, osteopenia, and left convexity lumbar scoliosis	
	Panoramic radiograph of LL	23/06/2023	Shortening of 4 mm of the total length of the lower limb, valgus knees, widened proximal tibial metaphysis, and flattened tibial and femoral metaphysis.	
	AP and lateral foot X-ray	02/08/2023	Decreased bone density and metatarsals with proximal angle.	
Abdomen and Kidney	Total abdominal ultrasound	12/07/2021 07/07/2023	Without alterations	
	Renal and urinary tract ultrasound	16/12/2020 12/07/2021 28/02/2022	Kidneys of normal size, preserved cortico-medullary relationship, no abnormalities in the urinary tract	
	Creatinine	20/01/2021 28/02/2022 29/08/2022 13/07/2023 24/01/2024	0.3 mg/dL 0.34 mg/dL 0.32 mg/dL 0.36 mg/dL 0.34 mg/dL	 Preserved
	Microalbuminuria	20/01/2021 13/07/2023 24/01/2024	21.6 mg/dL 22.07 mg/dL 14.65 mg/dL	 Preserved
Cardiopulmonary	Transthoracic echocardiogram	12/01/2021 01/04/2022	Heart with normal structure and functionality	
	Chest X-ray	7/03/2022	Diaconar index suggesting enlargement and accentuation of the bilateral bronchial branch	
	Spirometry	24/06/2022	FVC 65%, FEV1/FVC 105%, FEF25-75: 57%. Mixed component with greater restrictive involvement	
ORL	Pharyngeal cavum radiograph	07/03/2022	Adenoid hypertrophy	
Hepático	Total bilirubin	29/08/2022	0.52 mg/dL	
	ALT AST		15 UI/L 27 UI/L	
Urinary GAGs	Quantitative urinary GAGs levels	28/09/2022	12.77 mg/Gags/mol 7.06 mg/Gags/mol 6.44 mg/Gags/mol 5.34 mg/Gags/mol 19.58 mg/Gags/mol* 10.73 mg/Gags/mol 6.99 mg/Gags/mol	
Thyroid	TSH T4L	16/12/2022	0.613 mUI/L 1.12 ng/dL	Preserved

LL: Lower limbs. AP: Anteroposterior. ORL: Otorhinolaryngological.

patient is in eleventh grade, with good academic performance and no difficulty in socializing, being periodically evaluated by a multidisciplinary team of specialists aiming for timely management of the disease.

Bioinformatics Analysis – *In Silico*

The variant identified in the patient with MPS IV-A is of the missense type and consists of the transition from cytosine to thymine at position 239, which modifies the protein by changing the amino acid from serine to leucine at position 80. The classification of clinical significance was performed using *in silico* bioinformatics technology to predict its functional effect: ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), Varsome (https://varsome.com/), Polyphen (http://genetics.bwh.harvard.edu/pph2/), Mutation Taster (http://www.mutationtaster.org/) PROVEAN (http://provean.jcvi.org/index.php), SIFT (https://sift.bii.a-star.edu.sg/) and FATHMM (http://fathmm.biocompute.org.uk/). Based on this, pathogenic clinical significance was established (Table 2).

Table 2. Bioinformatic analysis by *In-Silico* technology conducted by the authors.

Gen	Variant	ClinVar	Varsome	Polyphen	Mutation Taster	Provean	SIFT	FATHMM
GALNS	p.Ser80Leu	P	P	PP	P	P	NR	NR

P: Pathogenic, PP: Probably pathogenic, NR: Not reported.

Discussion

The *GALNS* gene is located on chromosome 16q24.3, has a sequence of 2339 nucleotides composed of 14 exons and 13 introns, with an approximate length of 50 kb and encodes a protein of 522 amino acids, also being considered a heterogeneous gene with constitutive expression [2]. This gene encodes the lysosomal enzyme N-acetylgalactosamine-6-sulfatase (EC: 3.1.6.4), a 120 kDa homodimer with two functional domains [2] and is expressed in 27 tissues of the body, predominantly in skeletal muscle, testicles, and lung [3]. Pathogenic variants in the GALNS gene are associated with MPS IV-A (OMIM # 253000), a recessive autosomal disorder, of low prevalence, characterized by partial degradation and excessive accumulation of GAGs, specifically KS and C6S [4].Within the pathophysiology of the disease, a wide variety of biological processes have been implicated through aberrant signaling pathways at the cellular level, including abnormal membrane composition with impaired vesicular trafficking and autophagy phenomena, followed by increased oxidative stress and pro-inflammatory cytokines that lead to mitochondrial damage, ultimately resulting in apoptosis of connective tissue [15].

The clinical presentation of MPS IV-A is very heterogeneous; however, its main findings derive from the musculoskeletal system as a consequence of the abnormality in the chondrogenesis process and the appearance of multiple disostoses due to incomplete bone mineralization [1]. It is noted that more than 70% of patients with this disease have initial clinical manifestations within the first 2-3 years of life [16,17,18]. In the presented case, the patient debuted at the age of 5 with a primarily skeletal phenotype, including short stature, lower limb dysmetria with limited walking ability, and genu valgum, in addition to the same affected line being observed during follow-up with the development of cervical spinal compression and joint deformity, frequent complications described in the literature.

Upon reviewing similar cases of MPS IV-A worldwide involving adolescent patients, the study by Cadena Arteaga et al. (2022) was found, which reports on 5 patients diagnosed with MPS IV-A, 4 of whom fall within the established age range. In these patients, the development of skeletal complications was evident despite having started enzyme replacement therapy (ERT), as observed through radiological methods, including dysplasia in the carpal bones, epiphyseal dysplasia of the radius, and in the femoroacetabular joint, dorsolumbar kyphosis, plastipondylia, spinal compression at the C2-C3 level, and Madelung deformity compatible with carpal tunnel syndrome, findings similar to our case; although visceromegaly was also described to a lesser extent [18].

Mucopolysaccharidosis type IV-A (MPS IV-A) is characterized by the absence of central nervous system involvement, and thus, cognitive and behavioral deficits are not typically observed [3]. In the present case, the patient exhibited normal neurological development and currently performs well in her academic activities, without any reported difficulties. Although the literature supports the lack of cognitive impairment, some studies have reported that patients with MPS IV-A may exhibit difficulties with gaze initiation and maintenance, as well as impairments in sustained attention when compared to the general population. These findings have been hypothesized to result from disrupted neuroaxonal connectivity due to glycosaminoglycan (GAG) accumulation and altered calcium signaling pathways [19–21].

Given this, it could be considered that attentional deficits might influence the type of educational support that patients with MPS IV-A require. However, there are currently no studies to substantiate this hypothesis, suggesting a potential area for future research.

More than 400 variants in the *GALNS* gene associated with MPS IV-A have been described. In the description of these, it was found that 65% are missense types, 8.1% are *nonsense* types, 7.2% are *splicing* types, 7.0% correspond to small deletions/insertions due to frame shift, and 4% are of the intronic 5'UTR and 3'UTR types [5]. Despite the heterogeneity of the *GALNS* gene, genotype/

phenotype associations have been made, indicating that point variants are usually related to attenuated phenotypes, while *missense* variants, deletions, and *splicing* variants are expressed as severe phenotypes [2].

In the presented case, the variant c.239C>T (p.*Ser80Leu*) was identified in homozygosis of the *GALNS* gene. It is known that serine is a polar amino acid with a hydroxyl group (-OH) in its side chain, allowing it to form hydrogen bonds and participate in polar interactions, while leucine is a non-polar amino acid with a branched aliphatic side chain, which due to its hydrophobic nature tends to be located inside proteins.

The substitution of serine for leucine at position 80 may affect the three-dimensional structure of the protein, directly impacting on its stability and functionality, as it could interfere with its enzymatic function or biological activity, in addition to potentially altering its ability to interact with ligands or other proteins. Regarding the impact on the stability and dynamics of the final protein, leucine may increase hydrophobicity within it, stabilizing it under certain conditions or potentially inducing structural stresses if it causes mismatches in the local structure. This variant has been associated with MPS IV-A and has been reported in multiple studies [1,22,23]. Its impact on the function of the *GALNS* protein has been experimentally evaluated, showing that it may result in less than 10% of normal activity [2,24]. Although the allele frequency of this variant is very low in population databases and its quality data are questionable, *in-silico* prediction tools predict its harmful effect on the protein and classify it as pathogenic.

The genotype–phenotype correlation in Mucopolysaccharidosis type IV-A (MPS IV-A) is essential for understanding the wide clinical variability observed among patients. Clinical manifestations such as short stature, primarily skeletal and connective tissue involvement, along with the complications described in this case, are indicative of a severe phenotype, consistent with previously reported cases harboring the same genetic variant [1].

In recent years, advancements in omics technologies have facilitated the identification of novel variants associated with MPS IV-A. Coupled with bioinformatics tools for in-silico prediction of functional effects and comprehensive clinical characterization of affected individuals, these developments have deepened our understanding of the disease. Such progress has enabled more precise diagnoses and the implementation of targeted therapeutic strategies. These include enzyme replacement therapy (ERT) and emerging personalized treatments such as allogeneic hematopoietic stem cell transplantation, substrate reduction therapy, gene therapy, nanomedicine, and pharmacological chaperones, all aimed at modifying the course of the disease and improving patients' quality of life [10].

Conclusion

The clinical presentation in patients with EDL is key to making an accurate diagnosis, management, and treatment. The identification of characteristic symptoms in this specific case allowed for a more precise evaluation, highlighting the relevance of a thorough clinical approach. Likewise, the diagnostic methods used, which included imaging analyses and enzymatic tests, were essential to establish the case of MPS IV-A; however, confirmation through molecular and bioinformatics studies was fundamental to ensure an accurate diagnosis by identifying the specific variant causing the disease and allowed for genotype/phenotype correlation to determine the severity of the case, which in turn was associated with a better prognosis.

Continuous monitoring of the patient is not only vital for tracking the progression of the disease and the response to treatment, but it also provides important data for clinical research and understanding the pathology in a broader context. This multidisciplinary approach highlights the need to collaborate with various specialists, including geneticists, orthopedic traumatologists, endocrinologists, and occupational therapists, to comprehensively address the complexities presented by MPS IV-A. The integration of new technologies and diagnostic approaches promises to revolutionize the care and treatment of rare diseases like MPS IV-A, thus reinforcing the need for a proactive and collaborative approach in healthcare.

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Confidentiality of data: The authors declare that no patient data appears in this article and that they have followed the protocols of their workplace.
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Author's Contribution

MAM, CACT and JSRB oversaw the literature review and writing of the manuscript. DAT contributed to the analysis and interpretation of genetic data. JMSS contributed to the critical review of the manuscript and final approval.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability

The dataset supporting the results of this case report was fully included within the article. No additional datasets were deposited in public repositories.

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