Cross-sectional Study

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The clinical and genotypic–phenotypic findings of mucopolysaccharidosis VI patients: an Iraqi single-study descriptive study

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Background: Maroteaux–Lamy syndrome (mucopolysaccharidosis type VI; MPS VI) is a chronic illness that causes progressive enlargement, inflammation, or scarring of several tissues and organs until their collapse. In most cases, an infant with MPS VI shows no symptoms. The early signs and symptoms of MPS VI in children often develop in the first few months of life. MPS VI affects various systems in the body, including the skeletal, cardiac, and respiratory systems. The authors aim in our study to describe the clinical and genotypic–phenotypic findings of MPS VI patients in 'children Welfare Teaching Hospital, Medical City Complex.'

Methods: The single-center study was conducted at the 'children Welfare Teaching Hospital, Medical City Complex' from November 2016 to May 2022. The research recruited 72 MPS VI patients from Iraq, all under 20. The authors investigated the sociodemographic characteristics, hematological lab results, gene-phenotype findings, and clinical features and evaluated the severity and progression of the MPS 6 disease.

Results: Seventy-two Iraqi MPS VI patients were involved in the study, and the average age of the study sample was 6.38 ± 3.4 (0.3–19). The consanguinity rate was 94.4%. In the research, females comprised 56.9% of the patients, and the *Z*-scores for body mass index and occipital-frontal head circumference were – 2.66 and 1.2. The fascial features at diagnosis, 'coarse facies' (90.3%), dysostosis multiplex (93%), short stature (94.4%), and recurrent respiratory infections (91.6%), were the most common clinical features among the enrolled patients. The most frequent mutation was (complementary DNA: c.753C > G, protein effect: p.(Tyr2*) or p.(Tyr251Term), and the codon cross-tabulation: premature stop codon, or homozygous stop nonsense mutation/exon N.3) (33/69 (47.82%)). Furthermore, a statistically significant correlation existed between lower weight and height readings and the progressed and severe stages of the MPS VI illness.

Conclusion: As the first research in Iraq with a sufficient sample size of MPS VI patients, the investigation presented important clinical and gene-phenotype findings and revealed the necessity for enhancing the diagnosis of MPS VI, including the updated molecular analysis and monitoring the multisystem parameters, aberrant comorbidities, and the progression and severity.

Keywords: lysosomal storage disease, Maroteaux–Lamy syndrome, MPS 6, mucopolysaccharidosis VI

Background

Mucopolysaccharidoses (MPS) are progressive multisystem lysosomal storage disorders (LSDs) defined by a lack of enzymes involved in glycosaminoglycan (GAG) breakdown. Maroteaux–Lamy syndrome (MPS VI) is an uncommon, hereditary, autosomal-recessive metabolic disorder caused by mutations in the ARSB (arylsulfatase B) gene located on chromosome 5q13-q14. It is determined by the absence of the lysosomal enzyme *N*-acetylgalactosamine 4-sulfatase (arylsulfatase B; ASB; EC 3.1.6.12), which stimulates one of the processes in the breakdown of GAGs dermatan sulfate (DS) and chondroitin 4-sulfate (CS)[1]. This causes a gradual buildup of these chemicals in lysosomes and the extracellular matrix, resulting in cell and tissue harm and a cascade of organ failure, leading to severe clinical symptoms[2]. In 1963, Pierre Maroteaux and Maurice Lamy described MPS VI as a unique dysostosis with increased urine chondroitin sulfate excretion[3]. More than 200 pathogenic nucleotide variations

HIGHLIGHTS

- Mucopolysaccharidoses (MPS) are progressive multisystem lysosomal storage disorders.
- There is no published research with a sufficient sample size about the clinical, genotypic, and phenotypic characteristics of MPS VI patients in Iraq.
- We involved 72 Iraqi individuals with MPS VI disease – all of them were under 20 years old.
- The most prevalent mutation among the 72 patients involved was c.753C > G/p.(Tyr2*) or p.(Tyr251Term).
- The height and weight were discovered to be inversely associated with both the severity and progression of the MPS VI disease.

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have been detected in the ARSB gene; most are missense mutations, indicating a significant molecular heterogeneity of MPS VI in several populations[4]. Global estimations reveal that the prevalence of MPS VI varies widely by sociodemographic characteristics, ranging from 0.0132 per 100 000 live births in Poland to 7.85 per 100 000 live births in Eastern Saudi Arabia[5,6].

Although various factors affect the incidence rates in different communities, people with higher levels of consanguinity are expected to show a higher prevalence of the illness[7]. Patients with mucopolysaccharidosis type VI suffer from severe clinical findings, including macrocephaly, corneal opacity, facial dysmorphism, degenerative joint disease, chest deformities, umbilical hernias, low height, and heart abnormalities[8]. The clinical phenotype with urine GAG levels of more than 100 g/mg creatinine in cultured fibroblasts or isolated leukocytes is a sufficient tool for diagnosing MPS VI. In families with an affected child, prenatal diagnosis is based mostly on lowered ASB activity, with known mutational analyses as a supporting factor for high-risk pregnancies. In high-income countries, the diagnosis of mucopolysaccharidoses is based on urine tests for excessive mucopolysaccharides and enzyme assays. However, these tests are not widely available in low-income countries like Iraq, and the diagnosis depends on clinical and radiological findings.

Regarding the differential diagnosis, multiple sulfatase deficiency, MPS I, II, IVA, and VII should all be considered[9]. The therapy of MPS VI aims to treat some of the disease's most severe features, such as continuous positive airway pressure (CPAP) for sleep apnea. However, palliative care is still used presently, alongside other treatments like bone marrow or hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT)[10]. ERT, which is accessible for a few sorts of mucopolysaccharidoses, requires week after week intravenous mixtures, making it troublesome for patients and especially their families[11]. Most MPS VI patients with both severe and attenuated symptoms have missense mutations, accounting for most MPS VI mutations. Nevertheless, genotype–phenotype associations are difficult to ascertain because of the many harmful nucleotide variations[12]. In addition, multiple technologies were established to evaluate the effects of certain mutations on the quantity and activity of the enzyme[13,14]. The association of genotype to phenotype and prediction of severity involve challenges because of the low frequency of homozygosity, high frequency of compound heterozygosity, insufficient identification of polymorphisms, and sporadic findings of several mutations on a single allele.

The objective of this study is to evaluate the whole characteristics of MPS VI in Iraqi patients and compare results with patients from different nations. There is currently unavailable published research with a sufficient sample size discussing the clinical, genotypic, and phenotypic characteristics of MPS VI patients in Iraq. Thus, we conducted this descriptive research among 72 Iraqi mucopolysaccharidosis VI patients to study their clinical and gene results.

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Methods and materials

Study design, setting, and participants

We conducted a retrospective descriptive study on a single Iraqi medical center. We collected data from patients' previous hospital records that were confirmed to have MPS VI. Our study was conducted from November 2016 to May 2022 at the children Welfare Teaching Hospital, Medical City Complex. We involved 72 Iraqi individuals with MPS VI disease – all under 20 years old. The research was conducted following the Helsinki Declaration of the World Medical Association.

Measures

The enzyme level and molecular analysis were performed to detect the diagnosis of MPS VI disease. Direct DNA sequencing was implemented to undertake a molecular examination of the ARSB gene on genomic DNA. There was a standard form for recording the patients' data, which was separated into five components as follows: (a) Baseline characteristics of the inquired patients include age, consanguinity, gender, number of siblings, number of affected siblings, patient order in the family, height, weight, body mass index (BMI), and occipital-frontal head circumference (OFC). (b) Hematological laboratories at admissions: hemoglobin, platelets, white blood cells, urea, creatinine, iron, total iron-binding capacity (TIBC), tropical spastic paraparesis (TSB), serum glutamic–oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and anaplastic lymphoma kinase (ALK). (c) The enrolled patients' genetic findings include exon number, the number of exons, complementary DNA (cDNA), protein effect, and codon cross-tabulation. (d) The clinical features include delayed growth, fascial features at diagnosis 'coarse facies', dysostosis multiplex, corneal clouding, inguinal hernia, umbilical hernia, other types of hernia, short stature, deafness, retinal abnormalities, refractive errors, glaucoma, flexion contracture at joints, adenoid hypertrophy, recurrent chest infections, sleep apnea and snoring, cognitive impairment, communicating hydrocephalus, abnormally shaped teeth, hepatomegaly, splenomegaly, spinal cord compression, abnormal thick skin, bladder problems, heart valves diseases, and other cardiac abnormalities. (e) Specialists conducted several clinical examinations to determine the severity and the course of the disease. These measures included lung function, joint range of motion and strength, and the 3-min and 6-min walk tests[15].

Statistical analysis

Statistical Package for the Social Sciences (version 11.5; SPSS, Chicago, Illinois) was used to perform statistical analysis. Statistically significant differences had P values less than 0.05. Categorical data were presented as frequencies and percentages, while numerical data were presented as means and standard deviations. We performed Shapiro–Wilk test to check the disruption type of the analyzed data (parametric or non). We used the chi-square (χ^2) test for categorical variables and the Kruskal–Wallis test for continuous variables to compare the severity and progression of MPS VI disease in subgroups: age, consanguinity, sex, number of siblings, number of ill siblings, patient order within the family, height, weight, Z-score BMI, and Z-score OFC. We performed binary logistic regression to analyze the statically association between having a poor prognosis or severe stage of the studied disease (dependent variable) with the other variables

(independent variable), which we involved two models (unadjusted and adjusted to all covariates).

Our study is reported according to the STROCSS criteria 2021[16]. We submitted the protocol of our work to the Research Registry UIN 'www.researchregistry.com', whose unique identifying number (UIN) is researchregistry9032.

Ethical approval

Written informed consent was obtained from the patients' parents/legal guardians for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. The Medical Ethics Committee of the Welfare Teaching Hospital Ethics committee approved the research protocol. Each patient's family has given their verbal approval for our research (IRB: SEP/2022/1).

Results

Sociodemographic baseline characteristics

The demographic features of the patients are summarized in Table 1. Seventy-two Iraqi patients were involved, with an average age of 6.38 ± 3.43. The consanguinity rate was 94.4%, and more than half of the patients (55.6%) had under three siblings, and less than half (47.2%) had no affected siblings. The height and weight of patients were 90.81 ± 13.6 and 14.95 ± 5.3, respectively. In addition, the *Z*-score of BMI and OFC were – 2.66 ± 1.00 and 1.24 ± 1.00, respectively (Table 1).

Table 1

Sociodemographic baseline characteristics of the inquired patients (*N* = 72).

Variable	Category	Frequency	%
Age (mean ± SD)		6.38 ± 3.43	
Gender	Male	31	43.1
	Female	41	56.9
Consanguinity	First cousin	53	73.6
	Second cousin	15	20.8
	Negative	4	5.6
Number of siblings	Under three	40	55.6
	Equal three or above	32	44.4
Number of affected siblings	0	34	47.2
	1	32	44.4
	2	5	6.9
	5	1	1.4
Patient order	1st	21	29.2
	2nd	19	26.4
	3rd	9	12.5
	4th	9	12.5
	5th	7	9.7
	6th	3	4.2
	7th	3	4.2
	8th	1	1.4
Height (mean ± SD)		90.81 ± 13.6	
Weight (mean ± SD)		14.95 ± 5.3	
Z-score: BMI[a] (mean ± SD)		– 2.66 ± 1.00	
Z-score: OFC[b] (mean ± SD)		1.24 ± 1.00	

[a]Body mass index.
[b]Occipital-frontal head circumference.

Clinical features among the inquired MPS six patients

About 40.3% of patients suffered from delayed growth, and almost all patients (90.3%), (93%), and (88.9%) had facial features at diagnosis of 'coarse facies,' dysostosis multiplex, and corneal clouding, respectively. Inguinal and umbilical hernias were reported among 15.3% and 36.1% patients. Less than half of the patients (44.4% and 47.3%) were affected by deafness and refractive errors, respectively. Nearly a third of patients (31.9% and 34.7%) were hit with flexion contracture at joints and splenomegaly. Mitral regurgitation was the most common cardiac defect (52, 72%) in the study patients, followed by mitral valve prolapse (32, 44%) and thick mitral valve. Tricuspid valve regurgitation and aortic regurgitation were also noticed among eight and seven patients, respectively (Table 2, Fig. 1).

Hematological profile of the involved MPS six patients

Regarding the hematological profile, the mean and the standard and standard deviation of hemoglobin, white blood cell count, and platelets were 11.9 ± 1.6, 9.4×10^6 ± 3.8, and 271.4 ± 97.5, respectively. However, SGOT, SGPT, and ALK tests had a mean and standard deviation of 30.1 ± 11.6, 22.4 ± 12.5, and 245.5 ± 204, respectively (Table 3).

Genotype–phenotype findings

Genotype–phenotype findings in patients with MPS VI

Molecular genetic analysis of a total of 72 patients was performed. The most frequent mutation was found in the genotype–phenotype data to be cDNA: c.753C > G, protein effect: p.(Tyr2*) or p.(Tyr251Term), and the codon cross-tabulation: premature stop codon or homozygous stop nonsense mutation/

Table 2

The clinical presentations of the mucopolysaccharidoses patients (*N* = 72).

Clinical features	Frequency	%
Delayed growth	29	40.3
Fascial features at diagnosis 'coarse facies'	65	90.3
Dystostosis multiplex	67	93
Corneal clouding	64	88.9
Inguinal hernia	11	15.3
Umbilical hernia	26	36.1
Other types of hernia	8	11.1
Short stature	68	94.4
Deafness	32	44.4
Retinal abnormalities	1	1.4
Refractive errors	34	47.3
Glaucoma	12	16.7
Flexion contracture at joints	23	31.9
Adenoid hypertrophy	52	72.2
Recurrent chest infections	66	91.6
Sleep apnea and snoring	58	80.6
Cognitive impairment	7	9.7
Communicating hydrocephalus	3	4.2
Abnormally shaped teeth	43	59.7
Hepatomegaly	33	45.8
Splenomegaly	25	34.7
Spinal cord compression	2	2.8
Abnormal thick skin	58	80.6
Bladder problems	4	5.6

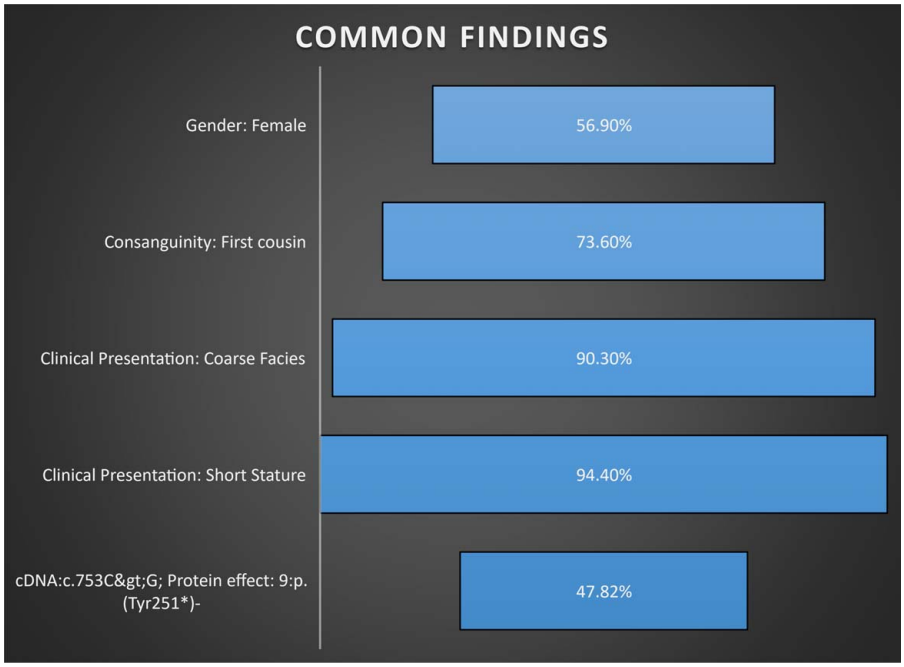

Figure 1. Summary of the overall most important findings of this study.

exon N.3 (33/69 (47.82%)). The allele of c.236G > A/p.(Gly79Glu) was repeated 1/69 (1.44%) in exon number 1, with a missense type of codon cross-tabulation; also, this exon had [cDNA: c.281C > A, protein effect: p.(ser94*)] in frequency 10/69 (14.4%) of gene 'ARSB'. Regarding exon number 2, there were two types of cDNA (c.253_365dup and c.323G > T) responsible for the protein effect [p.(Pro123Serfs*16) and p.(Gly108Val)] and codon cross-tabulation [Frameshift and Missense]; which, their gene 'ARSB' frequency was 1/69 (1.44%) and 2/69 (2.89%), respectively. Codon cross-tabulation [Heterozygous and Missense] who were produced by c.236G > A and c.236G > A, and c.753C > G was replicated 1/69 (1.44%) time for each one in exon 4. Among exon 5, the most recurrent gene 'ARSB' were 8/69 (11.59%) for c.1048A > T, p.(Leu321Pro), Missense followed by 4/69 (5.79%) for c.944G > A, p.(Arg315Gln), Missense and 2/69 (2.89%) for c.323G > T; c.962T > C, p.(9Gly108Val); p.(Leu321pro), Missense (Table 4).

Table 3

The hemotological profile of the involved patients at admission (*N* = 72).

Variable	Mean	Standard deviation	Normal range
Hemoglobin	11.9	1.6	Male: 13.8–17.2/female: 12.1–15.1 g/dl
White blood cell count	9.4×10^9/l	3.8	$4.5–11.0 \times 10^9$/l
Platelets	271.4	97.5	150–400/µl
Urea	21.2	7.5	6–24 mg/dl
Creatinine	0.3	0.14	0.74–1.35 mg/dl
Iron	66.2	31.5	60–170 µg/dl
TIBC	358.6	72.9	240–450 µg/dl
TSB	0.46	0.43	0.1–1.2 mg/dl
SGOT	30.1	11.6	8–45 U/l
SGPT	22.4	12.5	7–56 U/l
ALK	245.5	204	44–147 IU/l

ALK, anaplastic lymphoma kinase; SGOT, serum glutamic–oxaloacetic transaminase; SGPT; serum glutamic pyruvic transaminase; TIBC; total iron-binding capacity; TSB, tropical spastic paraparesis.

The difference between the subgroups of the severity and progression of the disease among MPS IV patients

We indicated a statistically significant difference between the consanguinity subgroups, with the patients with first cousin consanguinity and severe stage of the disease forming (72.2%). We determined that the patients slowly progressing with the disease have a higher mean age (10.3 ± 4.8, $P = 0.013$) than those rapidly progressing (5.96 ± 3.004). The patients with slowly progressing illness had higher weight, *Z*-score: BMI, and *Z*-score: OFC (22.42 ± 9.65, 1.027 ± 1.37, and 0.67 ± 0.706, respectively) than patients with rapidly progressing disease (14.15 ± 4.03, -0.11 ± 0.89, and -0.07 ± 1.003, respectively) ($P < 0.05$). (Table 5).

Multiple regression between the dependent variables and independent variables in MPS VI patients

Out of 10 predictors, we found that only height and weight measurements were statistically significantly correlated with the progressive and severe stages of the MPS VI disease ($P < 0.05$), which the patients who have a higher height and weight were less likely to have a severe stage [adjusted odds ratio (AOR) = 0.89 and 0.84, respectively] and rapid progression (AOR = 0.89 and 0.76, respectively) of the disease (Table 6).

Table 4

Genotype–phenotype findings in patients with MPS VI (Maroteaux–Lamy syndrome) (*N* = 69).

Exon	Gene 'ARSB'	cDNA	Protein effect	Codon cross-tabulation
Exon 1	1/69 (1.44%)	c.236G > A	p.(Gly79Glu)	Missense
Exon 1	10/69 (14.4%)	c.281C > A	p.(ser94*)	Premature stop codon
Exon 2	1/69 (1.44%)	c.253_365dup	p.(Pro123Serfs*16)	Frameshift
Exon 2	2/69 (2.89%)	c.323G > T	p.(Gly108Val)	Missense
Exon 4	33/69 (47.82%)	c.753C > G	9:p.(Tyr251*)–23:p.(Tyr251Term)	9: Premature stop codon–23: homozygous stop nonsense mutation
Exon 4	1/69 (1.44%)	c.236G > A	p.(Gly79Glu)	Missense
Exon 4	1/69 (1.44%)	c.236G > A and c.753C > G	p.(Gly79Glu) and p.(Tyr251*)	Heterozygous
Exon 4	1/69 (1.44%)	c.710C > A	p.(Ala237Asp)	Missense
Exon 5	1/69 (1.44%)	c.979C > T	p.(Arg327*)	Premature stop codon
Exon 5	1/69 (1.44%)	c.953A > T	p.(Lys318Ile)	Missense
Exon 5	1/69(1.44%)	c.943C > T	p.(Arg315*)	Premature stop codon
Exon 5	1/69 (1.44%)	c.935G > A	p.(Trp312*)	Premature stop codon
Exon 5	1/69 (1.44%)	c.1048A > T	p.(Ile350Phe)	Missense
Exon 5	2/69 (2.89%)	c.323G > T; c.962T > C	p.(9Gly108Val); p.(Leu321pro)	Missense
Exon 5	4/69 (5.79%)	c.944G > A	p.(Arg315Gln)	Missense
Exon 5	8/69 (11.59%)	c.962T > C	p.(Leu321Pro)	Missense

Discussion

The available literature on MPS VI epidemiology is limited to publications that solely report on birth prevalence. Furthermore, there is a dearth of research that characterizes the prevalence of MPS VI within the broader population. The incidence of the condition ranges from 1 in 43 261 births among Turkish immigrants in Germany to 1 in 1 505 160 births in Sweden, as reported in previous studies[17–20]. Our study highlights that the prevalence of MPS VI in Iraq has not been adequately investigated with a sufficient sample size. Additionally, it is worth noting that the consanguinity rate in Iraq is high[21,22], as we have reported in our research, with a rate of 94.4%. Maroteaux–Lamy syndrome is characterized by a spectrum of clinical manifestations that vary

Table 5

The difference between the subgroups of the severity and progression of the disease among MPS IV (Maroteaux–Lamy syndrome) patients.

		The Severity			*P*	The Progression		
Variable	Category	Attenuated	Intermediate	Severe		Rapid	Slowly	*P*
Age (mean ± SD)		9.4	11.7	6.26 ± 3.4	0.18	5.96 ± 3.004	10.3 ± 4.8	0.013
Gender	Male	1 (1.4%)	1 (1.4)	29 (40.3%)	0.2	28 (38.9%)	3 (4.3%)	0.99
	Female	0	0	41 (56.9%)		37 (51.4%)	4 (5.6%)	
Consanguinity	First cousin	1 (1.4%)	0	52 (72.2%)	0.001	48 (66.7%)	5 (6.9%)	0.54
	Second cousin	0	0	15 (20.8%)		14 (19.4%)	1 (1.4%)	
	Negative	0	1 (1.4%)	3 (4.2%)		3 (4.2%)	1 (1.4%)	
Number of siblings	Under Three	0	1 (1.4%)	39 (54.2%)	0.35	37 (51.4%)	3 (4.2%)	0.47
	Equal three or above	1 (1.4%)	0	31 (43.1%)		28 (38.9%)	4 (5.6%)	
Number of affected siblings	0	1 (1.4%)	1 (1.4%)	32 (44.4%)	0.89	30 (41.7%)	4 (5.6%)	0.7
	1	0	0	32 (44.4%)		29 (24.3%)	3 (4.2%)	
	2	0	0	5 (6.9%)		5 (6.9%)	0	
	5	0	0	1 (1.4%)		1 (1.4%)	0	
Patient order	1st	0	0	21 (29.2%)	0.76	19 (26.4%)	2 (2.8%)	0.31
	2nd	0	1 (1.4%)	18 (26.4%)		17 (23.6%)	2 (2.8%)	
	3rd	0	0	9 (12.5%)		9 (12.5%)	0	
	4th	1 (1.4%)	0	8 (11.1%)		6 (8.3%)	3 (4.2%)	
	5th	0	0	7 (9.7%)		7 (9.7%)	0	
	6th	0	0	3 (4.2%)		3 (4.2%)	0	
	7th	0	0	3 (4.2%)		3 (4.2%)	0	
	8th	0	0	1 (1.4%)		1 (1.4%)	0	
Height (mean ± SD)		112	129	89.97 ± 12.72	0.071	88.86 ± 10.43	109 ± 24.48	0.052
Weight (mean ± SD)		20	29	14.1 ± 5.1	0.1	14.15 ± 4.03	22.42 ± 9.65	0.007
Z-score: body mass index (mean ± SD)		0.45	1.68	− 0.03 ± 0.99	0.54	− 0.11 ± 0.89	1.027 ± 1.37	0.029
Z-score: OFC (mean ± SD)		− 0.08	0.84	− 0.01 ± 1.009	0.24	− 0.07 ± 1.003	0.67 ± 0.706	0.0045
Enzyme level (mean ± SD)		1.7	2.6	0.81 ± 1.08	0.159	0.812 ± 1.09	1.24 ± 1.13	0.13

Chi-square (χ^2) test for categorical variables and Kruskal–Wallis test for continuous variables.

Table 6

Multiple regression between the dependent variables (Having a severe stage of the disease/Having a rapid progression of the disease) and independent variables (Sociodemographic baseline co-varieties) among the MPS VI (Maroteaux–Lamy syndrome) patients.

		The Severity		The Progression	
Variable	Category	AOR[a], 95% CI: lower–upper; *P*	COR[b], 95% CI: lower–upper; *P*	AOR[a], 95% CI: lower–upper; *P*	COR[b], 95% CI: lower–upper; *P*
Age (mean ± SD)	–		0.7, 95% CI: 0.55–1.06; 0.6	0.52, 95% CI: 0.17–1.6; 0.25	0.7, 95% CI: 0.54–0.91; 0.05
Gender	Male	Ref			
	Female	–	–	0.65, 95% CI: 0.028–15.2; 0.79	0.99, 95% CI: 0.2–4.7; 0.99
Consanguinity	First cousin			Ref	
	Second cousin	–	–	0.49, 95% CI: 0.008–31.87; 0.74	1.4, 95% CI: 0.15–13.5; 0.74
	Negative	–		–	0.31, 95% CI: 0.027–3.5; 0.35
Number of siblings	Under three			Ref	
	Equal three or above	–	0.79, 95% CI: 0.04–13.2; 0.87	–	0.56, 95% CI: 0.11–2.7; 0.48
Number of affected siblings	0			Ref	
	1	–	–	–	1.28, 95% CI: 0.26–6.2; 0.75
	2	–		–	–
	5	–		–	
Patient order	1st	Ref			
	2nd	–	–	–	–
	3rd	–		–	
	4th	–		–	
	5th	–		–	
	6th	–		–	
	7th	–		–	
	8th	–		–	
Height (mean ± SD)		–	0.89, 95% CI: 0.81–0.97; 0.015	1.2, 95% CI: 0.6–2.2; 0.58	0.89, 95% CI: 0.83–0.96; 0.004
Weight (mean ± SD)		–	0.84, 95% CI: 0.71–0.99; 0.043	0.31, 95% CI: 0.0008–0.12; 0.53	0.76, 95% CI: 0.63–0.93; 0.008
Z-score: body mass index (mean ± SD)		–	0.41, 95% CI: 0.12–1.36; 0.14	–	0.43, 95% CI: 0.14–0.78; 0.12
Z-score: OFC (mean ± SD)		–	0.63, 95% CI: 0.12–3.2; 0.58	0.509, 95% CI: 0.06–3.9; 0.51	0.35, 95% CI: 0.12–1; 0.58
Enzyme level (mean ± SD)		–	0.46, 95% CI: 0.17–1.23; 0.12	0.31, 95% CI: 0.04–2.5; 0.28	0.73, 95% CI: 0.38–1.3; 0.32

[a]Adjusted odds ratio.
[b]Crude odds ratio.
OFC, occipital-frontal head circumference.

in severity, encompassing notable osteoarticular system dysfunction, dysostosis multiplex, reduced stature, and motor impairment. In addition, there was a high prevalence of ocular manifestations characterized by general corneal clouding, as well as signs related to the ear, nose, and throat (ENT). Furthermore, MPS VI is characterized by supplementary symptoms, including organomegaly and cardiorespiratory dysfunction. Some brain abnormalities have been identified, including white matter lesions, perivascular spaces, communicating hydrocephalus, and ventricular enlargement[1,2,3]. The most frequent clinical findings among the patients in our research were fascial characteristics 'coarse facies' (90.3%), dysostosis multiplex (93.4%), short stature (94.4%), recurrent respiratory infections (91.6%), and corneal clouding (88.9%). In contrast, the least frequent clinical findings included retinal abnormalities (1.4%), communicating hydrocephalus (4.2%), spinal cord compression (2.8%), and bladder issues (5.6%). A Brazilian study of four children with MPS VI that was followed up for 6 years found that all patients were short-statured and had coarse facies, and three patients had corneal clouding throughout the follow-up period[24]. Another research that was carried out in the United States over 15 years found that the most prevalent clinical findings were abnormal visual acuity (78.6%) and valve issues (90.0%)[2,5]. Furthermore, according to Germanic research that examined the clinical characteristics of patients with a mild stage of progressive mucopolysaccharidosis VI, depression, ocular clouding, respiratory issues, ENT rehabilitation, and valve defects were the most often seen presenting findings in the study population[26]. Regarding the genotype–phenotype results in MPS VI patients, a huge number of ARSB gene mutations, mostly missense, have been discovered as underlying MPS VI, and their heterogeneity makes interpreting the disorder a major challenge[27]. The diagnosis of MPS VI is confirmed by molecular genetic testing of the ARSB gene, which permits the discovery of disease-associated variations. Molecular testing should be done on both parents to ensure that the variations are on different chromosomes (segregation analysis) and, if only one variant is found, to prove the presence of homozygosis or to demonstrate the existence of

significant deletions. Also, the outcomes of the molecular analysis in the proband and both parents are helping to support genetic counseling, particularly in cases of preconception or prenatal testing, in families with MPS VI patients[1,6,28]. In our study, we defined that the most common mutation among the patients was on exon 4 (cDNA: c.753C > G, protein effect: p.(Tyr2*) or p.(Tyr251Term), and the codon cross-tabulation: premature stop codon or homozygous stop nonsense mutation) (33/69 (47.82%)), following on exon 5 (cDNA: c.962T > C, protein effect: p.(Leu321Pro), and the codon cross-tabulation: missense) (8/69 (11.59%)), on the exon 1 (c DNA: c.281C > A, protein effect: p.(ser94*)), and the codon cross-tabulation: premature stop codon (10/69 (14.4%)), and on exon 5 (cDNA: c.962T > C, protein effect: p.(Leu321Pro), and the codon cross-tabulation: missense) (8/69 (11.59%)). In contrast, 28 distinct variants were found in a Russian cohort of 68 individuals, with the most prevalent mutations being NM 000046.5: c.304C > G, NM 000046.5: c.941T > C, NM 000046.5: c.533A > G, NM 447 456del10, and NM 000046.5: c.990 1003del14, which NM 000046.5: c.990 1003del14 were identified in the severely affected patients[8]. However, since practically all of the patients in our research were in the severe stage of the MPS type 6 illness, we could not determine the mutations attached to this stage. In contrast, the lower weight and height among the included patients were associated with rapid disease progression and the severe stage of the MPS 6 disease. Similar results were found in research conducted in Taiwan, which showed that lower height and weight values are relevant to almost all types of MPS disease, specifically the severe stages[29]. Additionally, in agreement with our results, an Iraqi investigation of 16 MPS VI patients from the Hivi Pediatric Hospital in Duhok found that the majority of the patients carried the mutation c.962T > C (p.(Leu321Pro)). In contrast, others had c.585T > A (p.(ASP195Glu)) mutations, c.[585T > A];[753C > G] [Asp195 Glu];[Tyr251 Ter], and one patient had c.[288C > A];[962T > C] (p.[Ser96Arg];[Leu321Pro]) mutations, and all of the included patients showed coarse facial characteristics[30]. Saudi research discovered an association between high urine GAG levels and clinical indicators of an illness progressing more rapidly, such as short height, a lower body weight, and decreased ability as assessed by a 6-min walk. As a result, this biochemical measure was promoted as a crucial indicator for the severity and evaluation of MPS VI patients[31]. In conclusion, the published research on the genetic results and clinical characteristics in various countries, such as Russia[8], Saudi Arabia[31], the United States of America[1], etc., have provided varying findings. As a result, clinical studies with large sample sizes are needed to establish the actual manifestations of MPS VI patients and understand the elements consistent with the illness severity and recurrence. Considering current improvements in the illness's diagnostic and therapy approaches, early detection and precise diagnosis of this uncommon LSD are required for a better and more successful result. Inside this specific high population, newborn screening for MPS VI should be promoted. This study has certain limitations, such as the incapability to interpret clinical outcomes by surveilling the significant changes in clinical features, vital signs, and multisystem parameters and defining therapeutic strategies due to the insufficient medical infrastructure in Iraqi hospitals and not adhering to the recent criteria for the diagnostic procedures, and not perform the necessary, updated genetic analysis for the infrequent illnesses such as the MPS VI because the absence of sufficient financial sources. Secondly, our patients had progressed disease and were at a severe stage, making it difficult to demonstrate a causal association between the associated factors, especially the identified mutations. Finally, we could not measure the severity of the MPS VI condition using various criteria for exact assessment.

Given that Iraq is classified as a low-income country, the process of diagnosing MPS in this context may present certain challenges. The diagnosis and screening of MPS necessitates access to expensive equipment and resources. On a more general note, improving access to chronic illness profiling and oncological pathology, especially in low-income countries, through the availability of relevant equipment will guarantee a deeper understanding of such diseases[32]. In addition, developing countries suffer from limitations to diagnose chronic diseases; these limitations may include doctors' inadequate awareness and knowledge, the rarity of specialized centers, and the deficiency of genetic testing kits and materials due to expensiveness. Thus, we believe that a cooperative plan between health departments, health providers, patients, and the community is vital to challenge these limitations and help aid the diagnosis process of overall oncological, immune, and chronic diseases, especially in children[33]. There is no doubt that recent advancements in medicine, especially molecular, immunological, and pharmacological areas, have indeed assisted in diagnosing rare diseases. However, these resources and applications are almost exclusively available in high-specialist and funded centers. This limitation of such methods is a problem that faces both oncological and non-oncological tests. Thus, for the unprivileged centers, cooperation and proper communication with advanced centers and authorities are vital to supply the minimum requirements of resources until a sustainable method to deliver diagnostic tools is established[34].

It is recommended that local entities establish communication channels with international organizations such as the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) in order to expedite the implementation of solutions through various programs, including the Essential Diagnostics List and Priority Medical Devices initiatives. Furthermore, it is vital to highlight the importance of funding, enhancement of infrastructure, augmentation of human resources, and formulation of national policies to establish the employment of diagnostics based on evidence, thus guaranteeing optimal outcomes in patient care.

The most prevalent mutation among the 72 patients involved was c.753C > G/p.(Tyr2*) or p.(Tyr251Term), and both height and weight were discovered to be inversely associated with both the severity and progression of the MPS VI disease. More longitudinal studies are required to understand the precise contributors to the severity and progression of MPS VI illness, particularly the genetic findings for distinct follow-up periods.

Ethical approval

The Welfare Teaching Hospital Ethics committee provided ethical approval for the study (IRB: SEP/2022/1), and we confirm that all experiments were performed in accordance with the Declaration of Helsinki.

Consent

Written informed consent was obtained from the patient's parents/legal guardians for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

S.B.A.W.: made significant contributions to the conceptualization, writing, and critical assessment; S.S.: formal analysis and writing; R.F.T.: proofreading, reviewing, and supervising. All authors worked together to draft and edit the finished version. The manuscript's final version has been approved by all authors.

Conflicts of interest disclosure

There are no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Research Registry.
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Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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