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Clinical and genetic spectrums of Mucopolysaccharidosis type IV in Duhok city, Kurdistan region, Iraq

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Abstract

Mucopolysaccharidosis type IV also known as Morquio syndrome is a rare autosomal recessive lysosomal storage disorder due to deficiency of either N-acetyl-galactosamine-6-sulfatase (type A) or deficiency of beta-galactosidase (type B) which results in damages of bones, cartilages, eye corneas, skin and connective tissue. The objective of this study was to explore the relationship between specific gene mutations (c.860C>T, c.421T>A, c.1196delA) and clinical manifestations in patients with mucopolysaccharidosis type IV (MPS IV. The study was conducted at Heevi Tertiary Hospital in Duhok, Iraqi Kurdistan, till the period of September 2024, it involved 10 patients with confirmed MPS IV. Data on demographics, family history, consanguinity, skeletal, intelligence, and genetic mutations were collected. Results showed that mean age at diagnosis of 7.94 years, with females predominating. Consanguinity and family history were common. Short stature, macrocephaly, fatigue, generalized pain, and various skeletal abnormalities such as dysostosis multiplex and others. Hip dysplasia was present in 50% of patients, while intelligence was normal in most. The most frequent genetic mutation was c.860C>T, followed by c.421T>A and c.1196delA. Biochemical and hematological parameters were within normal ranges, but growth retardation was evident. Geographic clustering of mutations was noted, with c.860C>T prevalent in Zakho and c.1196delA exclusive to Akre. In conclusion, the study highlights the severe phenotypic expression associated with these mutations and underscores the influence of consanguinity and regional genetic predispositions. These findings emphasize the need for targeted genetic counseling and population screening programs in high-risk areas.

Keywords: Morquio syndrome; Mucopolysaccharidosis type IV; rare diseases; genetic mutations; Lysosomal storage diseases.

1. Introduction

Mucopolysaccharidosis type IV (Morquio A syndrome) is a rare autosomal recessive metabolic disorder resulting from mutations in the GALNS gene or GLB1. Typically, these mutations are homozygous. Other mutations are compound heterozygous. The result of these mutations is deficiency in the enzyme N-acetylgalactosamine-6-sulfatase (MPS-IVA) or of β-galactosidase (MPS-IVB). Consequently, degradation of keratan sulfate is impaired leading to intralysosomal accumulation of glycosaminoglycans, such as keratan sulfate (KS) and chondroitin-6-sulfate, and causing abnormal skeletal development and additional symptoms [1].

Most of these patients are normal at birth, and later on develop features of the disease with skeletal dysplasia after accumulation of GAGs. Then organ- and tissue-specific related pathologies start to develop. Non-skeletal manifestations of this disease may include eye involvement due to accumulation of GAG in sclera, retina, cornea and even optic nerve leading most frequently to mild corneal clouding. Teeth eruption is delayed leading to small teeth with thin enamel and frequent dental caries. Hepatomegaly, which is smooth and non-tender, is an occasional finding. Cardiac valves may be involved. Additionally, odontoid process instability and ligamentous laxity are consistent features, posing a risk of severe atlantoaxial instability and potential dislocation, which can be life-threatening [2]. Most individuals with MPS IV typically maintain normal intellectual abilities. However, the condition often leads to progressive physical limitations, with many requiring wheelchair assistance in their teenage years. Life-threatening complications may arise from respiratory causes represented by upper airway obstruction, respiratory failure due to diaphragm and chest wall or cardiac complications of valve involvement, or spinal cord compression [3, 4]. The definitive diagnosis will be confirmed by direct enzyme assay on blood leukocytes or skin fibroblasts then the type of genetic mutation is ordered to distinguish type A from type B [5]. As DNA technology has advancements, new treatments such as enzyme replacement have been found for this disorder with the FDA-approved Naglazyme® (Galsulfase) in May 2005. Studies have demonstrated significant improvement in overall health status and reduction in disease severity following early initiation of enzyme replacement therapy [6]. In our locality, there have been no comprehensive studies on MPS

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IV focusing on the relation of symptoms to specific genetic mutations. So I found it crucial to do this study with complete data of patients with rare diseases to answer the questions for instance whether some genetic mutations are linked with more severe clinical manifestations or not. The present study was conducted to investigate the association between specific genetic mutations (c.860C>T, c.421T>A, c.1196delA) and clinical phenotypes in patients with skeletal dysplasia, to investigate the role of consanguinity and family history in disease transmission and severity and also to analyse the biochemical and hematological profiles of patients and correlate them with genetic variants.

2. Materials and methods

2.1. Study Design and Setting

A cross-sectional observational study was conducted at Heevi Tertiary Hospital in Duhok Governorate in Iraqi Kurdistan in the period till the 1st of September 2024.

2.2. Ethical Considerations

Ethical approval was obtained from the general directorate of Health of Duhok granted permission for research (14005024-0001 on 14 May 2024). Written informed consent was obtained from the parents or guardians of all participants for the use of their medical records, clinical and genetic data and research publications. Patient confidentiality was maintained by anonymizing all data.

2.3. Participants and Clinical Data Collection

The study included 10 children diagnosed with MPS IV. From all participants clinical features were determined including family history, consanguinity, skeletal, neurologic features and intelligence, Anthropometric measures were measured; Height was measured without shoes using a portable stadiometer; weight was measured in light clothing using a digital Heine portable scale then CDC charts were used to establish percentiles.

2.4. Biochemical Analysis

For correct diagnosis, tandem mass spectrometry using dried blood spots was used to determine enzyme level and genetic study by ARCHIMED Life Laboratories, Vienna, Austria, Europe. From each of the analyses, a blood sample was taken to determine the laboratory tests such as blood count and morphology, liver and renal function test, serum electrolytes, Vit D3, Serum Ca, Spo4, and Alkaline phosphatase.

2.5. Statistical analysis

Demographic data, genetic mutations and laboratory tests were collected and then all data were entered and analyzed by SPSS version 27. Descriptive statistics were performed to find the mean and standard deviations and frequency (%). The continuous variables were presented as mean±SD with minimum and maximum values and categorical variables were presented as frequency (%). It was determined that the hypothesis was statistically significant if the p-value was less than 0.05.

3. Results

3.1. Sociodemographic, Clinical, and Genetic Characteristics of the Study Population

As seen in Table 1, the study cohort comprised 10 patients with MPS IV, with a mean age at diagnosis of

Table 1. Demographic, Clinical, and Genetic Characteristics of the Study Population.

Variable		N. (%)
Age categories	3- < 6 Years	3 (30%)
	6-< 9 years	4 (40%)
	9-12 years	3 (30%)
Gender	Male	4 (40%)
	Female	6 (60%)
Address	Zakho	5 (50%)
	Duhok	2 (20%)
	Akre	3 (30%)
Family history	Yes	7 (70%)
	No	3 (30%)
Consanguinity	Positive	9 (90%)
	Negative	1 (10%)
Short stature	Short stature	10 (100%)
Macrocephaly, Fatigue, Generalized pain	Yes	8 (80%)
	No	2 (20%)
Wheelchair	Yes	3 (30%)
	No	7 (70%)
Dysostosis multiplex, Joint stiffness, Genu valgum	Yes	7 (70%)
	No	3 (30%)
Pectus carinatum	Yes	7 (70%)
	No	3 (30%)
Kyphosis scoliosis	Yes	7 (70%)
	No	3 (30%)
Hip Dysplasia	Yes	5 (50%)
	No	5 (50%)
Intelligence	Yes	9 (90%)
	No	1 (10%)
Cervical spinal cord compression	Yes	3 (30%)
	No	7 (70%)
Carpal tunnel syndrome, Communicating, Hydrocephalus	Yes	4 (40%)
	No	6 (60%)
Gene Mutation type	c.860C>T (p. (Ser287Leu))	5 (50%)
	c.421T>A(P.(Trp 141Arg))	3 (30%)
	c.1196delA (p.(Lys399ArgfsTer42))	2 (20%)

7.94 years. Females were more numerous than males in this group, and most participants were from Zakho, followed by Akre. A significant proportion of the cohort had a family history of MPS IV, with a high prevalence of consanguinity reported. Short stature was a universal finding among the patients. Common clinical manifestations included macrocephaly, fatigue, generalized pain, and skeletal abnormalities such as dysostosis multiplex, joint stiffness, and genu valgum. Additional findings included pectus carinatum and kyphoscoliosis, with hip dysplasia present in half of the patients. The majority of the patients exhibited normal intelligence. The most frequent genetic mutation identified was c.860C>T (p.(Ser287Leu)), followed by c.421T>A (p.(Trp141Arg)) and c.1196delA (p.(Lys399ArgfsTer42)) (Table 1).

3.2. Clinical and Biochemical Parameters in the Study Population

It is noticed that biochemical and hematologic parameters (liver function tests, renal function tests, complete blood count, serum calcium, serum vitamin D level) are within normal ranges however weight and height metrics are suggestive of growth delay. As listed in Table 2.

3.3. Distribution of Demographic Data by Gene Mutation

The c.860C>T mutation is more prevalent in two age groups; 3-6 and 9-12 years, while c.1196delA is exclusively found in the 6-9 age group. c.860C>T is predominant in Zakho. c.421T>A is found in Duhok and Akre. c.1196delA is exclusive to Akre. c.1196delA is associated with a positive family history and consanguinity (Table 3).

3.4. Distribution of skeletal abnormalities and associated genetic mutations

It is seen that short stature is seen in all patients, regardless of mutation type. Macrocephaly, fatigue, and generalized pain were most prevalent in c.1196delA and c.860C>T. Dysostosis multiplex, joint stiffness, and genu valgum are common in c.860C>T and c.1196delA. Pectus carinatum and kyphosis scoliosis are prevalent across all mutations. Hip Dysplasia is most common in c.1196delA and c.421T>A. (Table 4).

3.5. Results of biochemical and hematological parameters and associated genetic mutations

In Table 5, c.1196delA shows higher WBC counts and platelet counts. c.421T>A has slightly elevated liver enzymes (SGPT). c.860C>T displays higher blood urea and creatinine. c.1196delA has lower serum calcium and vitamin D.

4. Discussion

This study of 10 patients with MPS IV has explored genotype correlation with clinical features of the individuals included. All of the patients in the present study had severe phenotypes. Similarly, Leong HY and his colleagues in Malaysia reported 21 patients with severe presentations [7]. Short stature was universal in our patients - and deserves to follow special growth charts specific to them- similar to what has been observed by Cárdenas JM et al.[8]. and by Vu CD et al.[9]. and Montano et al. (2008) [10]. Skeletal manifestations like joint stiffness, hip dysplasia, genu valgum, and kyphoscoliosis were prevalent and common in our patients identical to studies in Italy[11], and Latin America [12]. and by Montaño A. M. et al (2007) [13]. Cervical cord compression was noted in our patient with a similar percentage recorded in Malaysia by Leong HY et al.[7]. but wheelchair-bound individuals were lower compared to the same study. Intelligence was normal in majority of patients in line with Cárdenas JM et al.[8].

Common mutations from the most common in our studies were c.860C>T (p. (Ser287Leu)) in agreement with Tomatsu et al. (2004) [14], c.421T>A(P. (Trp 141Arg)) same as Montaño et al. (2007) [13]. and c.1196delA (p.(Lys399ArgfsTer42)) same as Sukegawa et al. (2000) [15]. Matched with identified gene mutations documented by Cárdenas JM et al. [8], Vu CD et al. (9). while other mutations which are common in other stu-

Table 2. Descriptive Statistics of Clinical and Biochemical Parameters in the Study Population.

Variables	Mean± (Std)	Minimum	Maximum
Age	7.94 ± (2.97)	3.80	12.60
Weight	13.70 ± (1.25)	12	16
Height	90.35 ± (3.33)	85.0	94.0
SGPT	11.90 ± (2.6)	9	17
SGOT	31.60 ± (4.3)	25	41
Hb	12.28 ± (1.25)	10.0	14.0
WBC counts	8488.89 ± (2443.07)	6000	14000
Platelet counts	300.70 ± (98.14)	134.0	510.0
Blood urea	34.50 ± (13.70)	16	62
Creatinine	0.515 ± (0.36)	.14	1.00
Serum sodium	138.00 ± (2.00)	134	141
Serum potassium	4.49 ± (0.46)	3.90	5.10
Serum calcium	9.39 ± (0.84)	7.80	10.13
Serum chloride	106.30 ± (1.41)	104	108
alkaline phosphates	148.81 ± (27.98)	112.00	194.00
Vitamin D	21.49 ± (8.23)	11.00	33.00
Random blood sugar	91.10 ± (16.64)	70	131

Table 3. Distribution of Demographic data by Gene Mutation.

Variables		Gene mutation			Total N=10 (%)	P value
		c.860C>T (p. (Ser287Leu))	c.421T>A(P.(Trp 141Arg))	c.1196delA (p.(Lys399ArgfsTer42))		
		N=5 (%)	N=3 (%)	N=2 (%)		
Age categories	3- < 6 years	2 (40%)	1 (33.3%)	0 (0%)	3 (30%)	0.4
	6-< 9 years	1 (20%)	1 (33.3%)	2 (100%)	4 (40%)	
	9-12 years	2 (40%)	1 (33.3%)	0 (0%)	3 (30%)	
Gender	Male	2 (40%)	1 (33.3%)	1 (50%)	4 (40%)	0.9
	Female	3 (60%)	2 (66.7%)	1 (50%)	6 (60%)	
Address	Duhok	0 (0%)	2 (66.7%)	0 (0%)	2 (20%)	< 0.005
	Zakho	5 (100%)	0 (0%)	0 (0%)	5 (50%)	
	Akre	0 (0%)	1 (33.3%)	2 (100%)	3 (30%)	
Family history	Yes	4 (80%)	1 (33.3%)	2 (100%)	7 (70%)	0.2
	No	1 (20%)	2 (66.7%)	0 (0%)	3 (30%)	
Consanguinity	Positive	4 (80%)	3 (100%)	2 (100%)	9 (90%)	0.5
	Negative	1 (20%)	0 (0%)	0 (0%)	1 (10%)	
Age of diagnosis	1	2 (40%)	0 (0%)	0 (0%)	2 (20%)	0.3
	2	2 (40%)	1 (33.3%)	0 (0%)	3 (30%)	
	3	1 (20%)	2 (66.7%)	2 (100%)	5 (50%)	

Table 4. Distribution of Skeletal Abnormalities and Associated Genetic Mutations.

Variables		Gene mutation			Total N=10 (%)
		c.860C>T (p. (Ser287Leu))	c.421T>A(P.(Trp 141Arg))	c.1196delA (p.(Lys399ArgfsTer42))	
		N=5 (%)	N=3 (%)	N=2 (%)	
Short stature	Short stature	5 (100.0%)	3 (100.0%)	2 (100%)	10 (100%)
Macrocephaly, Fatigue, Generalized pain	Yes	4 (80.0%)	2 (66.7%)	2 (100%)	8 (80%)
	No	1 (20.0%)	1 (33.3%)	0 (0%)	2 (20%)
Wheelchair	Yes	3 (60.0%)	0 (0.0%)	0 (0%)	3 (30%)
	No	2 (40.0%)	3 (100.0%)	2 (100%)	7 (70%)
Dysostosis multiplex, Joint stiffness, Genu valgum	Yes	4 (80.0%)	1 (33.3%)	2 (100%)	7 (70%)
	No	1 (20.0%)	2 (66.7%)	0 (0%)	3 (30%)
Pectus carinatum	Yes	2 (40.0%)	3 (100.0%)	2 (100%)	7 (70%)
	No	3 (60.0%)	0 (0.0%)	0 (0%)	3 (30%)
Kyphosis scoliosis	Yes	2 (40.0%)	3 (100.0%)	2 (100%)	7 (70%)
	No	3 (60.0%)	0 (0.0%)	0 (0%)	3 (30%)
Hip Dysplasia	Yes	1 (20.0%)	2 (66.7%)	2 (100%)	5 (50%)
	No	4 (80.0%)	1 (33.3%)	0 (0%)	5 (50%)
Cervical spinal cord compression	Yes	2 (40.0%)	0 (0.0%)	1 (50%)	3 (30%)
	No	3 (60.0%)	3 (100.0%)	1 (50%)	7 (70%)
Carpal tunnel syndrome, Communicating, Hydrocephalus	Yes	2 (40.0%)	1 (33.3%)	1 (50%)	4 (40%)
	No	3 (60.0%)	2 (66.7%)	1 (50%)	6 (60%)

dies are: p.R386C (c.1156C>T) by Tomatsu et al. (2004) [14]. p.R380S (c.1140G>T) by Montaño et al. [13]. and p.N164T (c.500A>C) by Ogawa et al. (1995) [16]. The high prevalence of consanguinity and family history suggests a genetic basis for the condition, with specific mutations linked to skeletal and growth abnormalities. The biochemical and hematological parameters are within normal ranges, but the low height and weight suggest growth retardation, possibly linked to genetic mutations. Geographic clustering, such as the prevalence of c.860C>T in Zakho and c.1196delA in Akre, highlights the influence of consanguinity and regional genetic predispositions. The high prevalence of familial cases underscores the need for targeted genetic counseling and population screening programs in high-risk areas. c.860C>T (p. (Ser287Leu)) was the most common mutation reported in our patients

Table 5. Descriptive Statistics of Clinical and Biochemical Parameters in the Study Population.

Variables	Genetic Mutation Type		
	c.860C>T (p.(Ser287Leu))	c.421T>A(P.(Trp 141Arg))	c.1196delA (p.(Lys399ArgfsTer42))
	Mean ± (Std).	Mean ± (Std).	Mean ± (Std).
Hb	12.4 ± (1.5)	12.0 ± (0.6)	12.5 ± (2.1)
WBC counts	7500 ± (1500)	7950 ± (1626)	11500 ± (3536)
Platelet counts	284.8 ± (51.8)	267.0 ± (115.4)	391.0 ± (168.3)
SGPT	11 ± (3)	14 ± (3)	11 ± (2)
SGOT	31 ± (6)	32 ± (2)	33 ± (2)
Blood urea	45 ± (11)	22 ± (7)	28 ± (6)
Creatinine	0.66 ± (0.42)	0.24 ± (0.05)	0.55 ± (0.40)
Serum sodium (S. Na)	138 ± (2)	137 ± (1)	141 ± (1)
Serum chloride (S. Cl)	106 ± (2)	106 ± (1)	106 ± (3)
Serum potassium	4.32 ± (0.54)	4.68 ± (0.23)	4.65 ± (0.64)
Serum calcium	9.33 ± (0.84)	9.91 ± (0.28)	8.80 ± (1.41)
alkaline phosphates	148.20 ± (32.80)	135.70 ± (25.10)	170.00 ± (8.49)
Vitamin D	23.12 ± (10.27)	20.10 ± (7.10)	19.50 ± (7.78)
Random blood sugar	91 ± (24)	96 ± (3)	84 ± (8)

in contrast to the finding of Zanetti et al who have found that c.953T>G (p.(Met318Arg)) was most commonly prevalent [17]. and in concordance with the findings of Bidchol et al.[18]. c.421T>A was the second most common mutation in our patients and has been associated with short stature, kyphoscoliosis, hip dysplasia, carpal tunnel syndrome, macrocephaly, and noncommunicating hydrocephalus. This type of mutation is among the most common mutations detected in Turkey by Bunge et al.[16] . This mutation also has been recorded by Tüysüz B et al. in two families with severe phenotype in one family and another one with intermediate phenotype [19]. The least reported mutation was c.1196delA which was associated with the most severe skeletal abnormalities.

The limitation of our study lies in its small size as it is the state for many rare conditions. All of our patients had severe features, probably those with mild or intermediate features were missed or undiagnosed.

5. Conclusions

This study provides critical insights into the clinical and genetic landscape of MPS IV within the Duhok region of Iraqi Kurdistan, highlighting the severe phenotypic expression associated with specific mutations, particularly c.860C>T, c.421T>A, and c.1196delA. The observed geographic clustering of these mutations, coupled with the high prevalence of consanguinity, underscores the influence of regional genetic predispositions on disease manifestation. The study emphasizes the need for targeted genetic counseling and population screening programs in high-risk areas to facilitate early diagnosis and management of MPS IV. Future research should focus on expanding the cohort to include more patients from all governorates of Iraq, as well as investigating other variables to provide a more comprehensive understanding of the disease.

Abbreviations

MPS IV: Mucopolysaccharidosis type IV, GAGs: Glycosaminoglycans, KS: Keratan sulfate, GALNS: N-acetylgalactosamine-6-sulfatase, GLB1:Beta-galactosidase, MPS IVA: Mucopolysaccharidosis type IVA, MPS-IVB: Mucopolysaccharidosis type IVB, FDA: Food and Drug Administration, Vit D3:Vitamin D3, Ca: Calcium, Spo4: Serum phosphate, WBC: White blood cell, SGPT: Serum glutamic-pyruvic transaminase, CDC: Centers for Disease Control and Prevention, SPSS: Statistical Package for the Social Sciences, SD: Standard deviation, DNA: Deoxyribonucleic acid

Conflicts of Interest

The author declares no conflicts of interest.

Consent for Publication

The original article is not under consideration by another publication, and its substance, tables, or figures have not been published previously and will only be published elsewhere.

Ethical Declaration and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethical Committee for Medical and General Health Research Ethics of the General Directorate of Health in Duhok (14005024-0001).

Informed Consent

Written informed consent has been obtained from all parents for using data's and publishing this paper.

Availability of data and materials

The data presented in this study are available on request from the corresponding author. email: azad.haleem@uod.ac

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