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Original Article

Physical features of Patients with Mucopolysaccharidoses and other correlated laboratorial examinations

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ABSTRACT

Background: Mucopolysaccharidoses (MPS) are genetic disorders of the catabolism of glycosaminoglycans (GAGs). MPS are categorized into different types; each type is caused by a deficiency in the activity of a specific lysosomal enzyme required for GAGs degradation[1]. This study was designed to identify the physical features, assay the enzymatic deficiency and examine the hematological pictures in patients with different types of MPS. ***Methods:*** This cross-sectional study was conducted on 16 MPS patients, in the Pediatric department at Zagazig University Hospitals.
Results: The age of children in the studied groups ranged between 7 to 17 years, height ranged between 88 to 120 cm, and weight range of 15 to 29 Kg but without statistically significant difference. There was statistically significant relation between type of MPS and urinary GACs**.** On doing Tukey's HSD (honestly significant difference) test, the difference was significant between type I and II. Also, between type II and IV-A. However, type IV-A did not differ from type VI or I. There was statistically significant relation between type of MPS and mental delay. Only patients with type I and II had mental delay. There was statistically non-significant difference between the studied groups with different types of MPS regarding complete blood count (CBC) except platelet and lymphocytic count. There was statistically non-significant difference between the studied groups with different types of MPS regarding liver function tests.
Conclusion: Diagnostic enzymatic assay in combination with different diagnostic tools as case history, physical features, hematological examination and liver function tests were essential for correct diagnosis and early interference.
Keywords: Physical Features, Mucopolysaccharidoses, Hematological investigations

INTRODUCTION

The mucopolysaccharidoses (MPS) comprise a group of inherited lysosomal storage disorders characterized by deficiencies in enzymes catalyzing the degradation of glycosaminoglycans (GAGs). glycosaminoglycans (GAGs) are linear unbranched polysaccharides, which normally found on the cell surface or in the extracellular matrix where their functions represent in hydration/water homeostasis, regulation of growth/remodeling, and inflammation**[2]** Depending on the enzyme deficiency, specific GAG(s) are accumulated in different cells, tissues, and organs, which result in complicated clinical ramifications ranging from central nervous system involvement to multiorgan

failure. Clinical features include cognitive impairment, hearing and vision loss, respiratory and cardiac involvement, organomegaly, skeletal and joint abnormalities, and short stature, within each of the MPS disorders there is a wide spectrum of clinical severity**[3]**. This study was designed to identify the physical features, assay the enzymatic deficiency and examine the hematological pictures, in patients with different groups (I (Hurler), II (Hunter), IV-A (Morquio), and VI (Maroteaux Lamy)) of mucopolysaccharidoses (MPS) in the Pediatric Department, Zagazig University Hospitals.

METHODS

Population or Subjects: Sixteen patients with MPS (11males and 5females; Patients age from 7 to 17 years) who were diagnosed with MPS types I, II, IVA, and VI, and who were under supervision at Zagazig University Hospital were enrolled in this study. MPS diagnosis was made on the basis of clinical data, determination of lysosomal enzyme activities. All had received Enzyme Replacement Therapy (ERT). Five Patients had done surgical Tonsillectomy. The diagnosis of MPS was confirmed by two-dimensional electrophoresis of urinary glycosaminoglycans and enzyme assay in serum, which were identified with MPS I, with MPS II, with MPS IV, and with MPS VI. Approval with number 6969 30-5-2021 was taken from the ethical committee and also ethical consent was taken from patients or their relatives included in the study. Severely affected patient on Mechanical Ventilation were excluded from this study. The research was carried out in compliance with the Code of Ethics of the World Medical Association (Decleration of Helsinki) for studies involving humans.

Inclusion criteria: The individuals with the following criteria were included to our study; Patients age from 7 to 17 years. Admission to the outpatient or the Enzyme Replacement Unit at Zagazig University Hospitals. Diagnosed as Mucopolysaccharidoses. Exclusion criteria: Severely affected patient on Mechanical Ventilation were excluded from our study.

Patients and controls underwent to full history taking (name, age, sex Height, Weight and ERT receiving) and clinical examination including (cough, dyspnea and wheeze), the age of onset, the duration of disease, and response to medication, current medications, previous hospitalization, and symptoms suggestive of other system affection.

Complete physical examination including the physical features of children and adolescents with different types of MPS including Mental delay, Coarse facies, Joint stiffness, Hirsutism, Skeletal abnormalities, Tonsillectomy, Visceromegaly and Surgical correction of inguinal hernia.

Full general examination including (Vital signs - Chest examinations and signs of respiratory distress - Physical growth was assessed for all children by determining the weight, height, body mass index (BMI)).

The diagnostic enzyme assays were selected for detection of Enzyme deficiency. Investigations included Complete blood count (CBC) as (Hgb (Hemoglobin), RBCs (Red blood cells) count, MCV (mean Corpuscular Volume), PCV (Packed Cell Volume), MCH (mean Corpuscular Hemoglobin), MCHC (mean Corpuscular Hemoglobin Concentration), Lymphocytes, Total WBCs (White blood cells) and Platelet count. Liver function tests as (Total bilirubin, Direct bilirubin, Indirect bilirubin, ALT (Alanine aminotransferase) and AST (Aspartate transaminase)).

Enzyme Activity Levels:

Determination of lysosomal enzymes activity levels in leukocytes was performed in National Research Institute, Dokki, Cairo. Lysosomal enzyme activity was measured in dried blood spots by fluorometry and tandem mass spectrometry.

Statistical Analysis:

The values were presented as means ± standard deviation (SD). The data were subjected to the statistical package for social sciences (SPSS-16.; Chicago, IL, USA) software and one-way Analysis of Variance (ANOVA) at 95 % level of confidence. Significant differences among the means were

determined by Tukey's Kramer HD test considering $P < 0.05$ as significant. All tests were two sided, P<0.05 was considered statistically significant, P<0.001 was considered highly statistically significant, and P≥0.05 was considered non statistically significant.

RESULTS

The clinical characteristics of children and adolescents with different types of MPS involved in the current study were presented in **Table (1**) (Number (No.) of patients =16). Where the age of children in the studied groups ranged between 7 to 17 years, height ranged between 88 to 120 cm, and weight range of 15 to 29 Kg. The IV-A (Morquio) group had the highest average age (11.5 ± 3.78 years), while the VI (Maroteaux Lamy) group had the highest average height (109 ± 9.64 cm), and the II (Hunter) group had the highest average weight (22.33 ± 5.77 Kg), respectively but without statistically significant difference.

There was statistically significant relation between type of MPS and urinary GACs. On doing Tukey HSD test, the difference was significant between type I and II. Also, the difference was significant between type II and IV-A. On the other hand, type IV-A did not differ from type VI or I **Table (2)** (No. of Patients) =16.

There was statistically significant relation between type of MPS and presence of mental delay. All patients with type IV-A and VI had no mental delay while all those with type I and II had mental delay. There was statistically non-significant difference between them regarding other clinical manifestations. **Table (3)** (No. of Patients) =16.

There was statistically non-significant difference between the studied groups with different types of MPS regarding hemoglobin, white blood cells, PCV, MCH, MCHC, or red blood cell count. There was statistically significant difference between the studied groups with different types of MPS regarding platelet count. On Tukey HSD comparison, the difference between type I and all of type II (p=0.018), type IV-A (p=0.016) and type VI (p= 0.012). while there was non-significant difference between each two individual groups. There was statistically significant difference between the studied groups with different types of MPS regarding lymphocytic count. On Tukey HSD comparison, the difference between type I and type VI (p= 0.023). Also the difference between type II and VI (p=0.011), while there was non-significant difference between each two individual groups **Table (4)**. (No. of Patients) =16.

There was statistically non-significant difference between the studied groups with different types of MPS regarding total, direct bilirubin, AST, ALT, or indirect bilirubin **Table (5)** (No. of Patients) =16.

Table 1. Clinical characteristics of children and adolescents with different types of MPS.

Criteria / Types of MPS	Age (Years)			Height (cm)			Weight (kg)		
	Min	Max	Mean ± SD	Min	Max	Mean ± SD	Min	Max	Mean ± SD
I (Hurler)	7	12	8.5 ± 2.38	88	115	102.25±11.18	17	24	20.5 ± 2.89
II (Hunter)	8	11	9.33 ± 1.53	93	115	103 ± 11.14	19	29	22.33 ± 5.77
IV-A (Morquio)	7	17	11.5 ± 3.78	97	110	103.17 ± 5.04	15	25	21 ± 3.52
VI (Maroteaux-Lamy)	8	13	10.33 ± 2.52	102	120	109 ± 9.64	17	25	20 ± 4.36
F	0.904			0.404			0.193		
p	0.468			0.753			0.899		

Min = Minimum, Max = Maximum, S.D = Standard Deviation MPS = Mucopolysaccharidosis, ERT = Enzyme Replacement Therapy

F One Way ANOVA test p>0.05 is statistically non-significant

Table 2. Enzyme deficiency in children and adolescents with different types of MPS.

Types of MPS		Galactoseamine 6 slfate sulftase (pmol/g.proth/h)	α-iduronidase (micromol/g.prot/h)	Iduronate Sulfatase (micromol/l/h)	Arylsulfatase-B (N-acetylgalactosamine sulfatase) (nmol/mg.prot/h)	Urinary GAGs (mg/mmol creatnine)	
I (Hurler)	Min		0.1			3.9	P1 <0.001**
	Max		0.4			14.7	
	Mean ± SD		0.25 ± 0.17			8.52 ±5.57	
II (Hunter)	Min			0		76.7	P2 <0.001**
	Max			1		94.9	
	Mean ± SD			0.67 ± 0.58		85.27±9.15	
IV-A (Morquio)	Min	50				3.9	P3 0.062
	Max	201.5				6.95	
	Mean ± SD	132.03 ± 76.53				4.92 ± 1.76	
VI (Maroteaux-Lamy)	Min		12		0.2	33.18	P4 0.002*
	Max		18.5		0.3	34.5	
	Mean ± SD		16.07 ± 3.54		0.25 ± 0.05	33.83±0.66	P5 0.519
F						27.15	
p						<0.001**	P6 0.346

Min = Minimum, Max = Maximum, S.D = Standard Deviation, MPS = Mucopolysaccharidosis, GAGs = Glucose Aminoglycans P1 difference between I and II p2 difference between type II and IV-A p3 difference between type IV-A and type VI p4 difference between type II and IV-A p5 difference between type I and IV-A p6 difference between type I and VI.

Table 3. The physical features of children and adolescents with different types of MPS.

Physical features \ Types of MPS		I (Hurler) (NO. = 4)		II (Hunter) (NO. = 3)		IV-A (Morquio) (NO. = 6)		VI (Maroteaux-Lamy) (NO. = 3)		χ^2	p
		NO.	%	NO.	%	NO.	%	NO.	%		
Mental delay	+ve	4	100	3	100	0	0	0	0	11.91	0.001**
	-ve	0	0	0	0	6	100	3	100		
Coarse facies	+ve	4	100	3	100	1	16.67	3	100	1.52	0.218
	-ve	0	0	0	0	5	83.33	0	0		
Joint stiffness	+ve	4	100	3	100	2	33.33	3	100	1.11	0.292
	-ve	0	0	0	0	4	66.67	0	0		
Hirsutism	+ve	4	100	3	100	0	0	3	100	2	0.157
	-ve	0	0	0	0	6	100	0	0		
Skeletal abnormalities	+ve	4	100	3	100	6	100	3	100	0	>0.999
	-ve	0	0	0	0	0	0	0	0		
Tonsillectomy	+ve	1	25	2	66.67	2	33.33	0	0	0.55	0.46
	-ve	3	75	1	33.33	4	66.67	3	100		

Surgical correction of inguinal hernia	**+ve**	1	25	1	33.33	1	16.67	0	0	0.768	0.38
	-ve	3	75	2	66.67	5	83.33	3	100		
Visceromegaly	**+ve** **H/S**	4	100	2	66.67	2	33.33	3	100	0.55	0.46
	H	0	0	1	33.33	0	0	0	0		
	-ve	0	0	0	0	4	66.67	0	0		

The percentage was calculated according to the total number of cases in each MPS types **p≤0.001 is statistically highly significant

NO. = number, MPS = Mucopolysaccharidosis, +ve = presence, -ve = absent,

H/S. = Hepatomegaly/Splenomegaly, H. = Hepatomegaly χ2chi square for trend test

Table 4. The CBC of children and adolescents with different types of MPS.

Types of MPS		**Hgb (g/dL)**	**RBCs count (× 10^6/µL)**	**PCV (%)**	**MCV (fL)**	**MCH (pg)**	**MCHC (g/dL)**	**Platelet count (× 10^3/µL)**	**Total WBCs (× 10^3/µL)**	**Lymphocytes (× 10^3/µL)**
I (Hurler)	**Min**	11.9	4.31	34.5	75.5	27	34.4	350	7.2	41
	Max	13.3	4.9	37.2	80	27.5	35.8	384	11.7	41.39
	Mean ± SD	12.6 ±0.99	4.61±0.42	35.85±1.91	77.75±3.18	27.25±0.35	35.1±0.99	367±24.04	9.45±3.18	41.2 ± 0.28
II (Hunter)	**Min**	11.4	3.1	30	71.4	23.11	31.3	250	6.2	41.8
	Max	12.1	4.22	36.4	115	36.7	36.2	251	9.2	42
	Mean ± SD	11.75±0.49	3.66±0.79	33.2 ± 4.53	93.2±30.83	29.91±9.61	33.75±3.46	250.5±0.71	7.7 ± 2.12	41.9 ± 0.14
IV-A (Morquio)	**Min**	12	4.54	40.8	78.4	23.6	30.1	213	4.8	43.9
	Max	13.2	5.6	43.9	86.7	27.5	30.3	262	6.8	47.6
	Mean ± SD	12.6±0.85[a]	5.07±0.75	42.35±2.19	82.55±5.87	25.55±2.76	30.2 ± 0.14	237.5±34.65	5.8 ± 1.41	45.75 ± 2.62
VI (Maroteaux-Lamy)	**Min**	11.4	5.2	34.7	60.7	23.1	19.9	243	5.6	32
	Max	12.1	5.72	37.4	71.4	32.4	32.9	249	9.2	33.4
	Mean ± SD	11.75±0.49	5.46±0.37	36.05±1.91	66.05±7.57	27.75±6.58	26.4 ± 9.19	246 ± 4.24	7.4 ± 2.55	32.7 ± 0.99
F		0.88	3.213	3.701	16.785	0.944	2.622	16.785	0.775	18.266
p		0.523	0.145	0.119	0.01*	0.499	0.187	0.01*	0.566	0.02*

F One Way ANOVA test p>0.05 is statistically non-significant.

Min = Minimum, Max = Maximum, S.D = Standard Deviation, MPS = Mucopolysaccharidosis, CBC = Complete Blood Count, Hgb = Hemoglobin, RBCs = Red Blood Cells, PCV = packed cell volume, WBCs = White Blood cells, MCV = Mean Corpuscular Volume, MCH = Mean Corpuscular Hemoglobin, MCHC = Mean Corpuscular Hemoglobin Concentration

Table 5. Liver function tests of children and adolescents with different types of MPS.

Types of MPS		Total bilirubin (mg/dL)	Direct bilirubin (mg/dL)	Indirect bilirubin (mg/dL)	AST (SGOT) (U/L)	ALT (SGPT) (U/L)
I (Hurler)	Min	0.45	0.09	0.34	19.78	12.31
	Max	1	0.21	0.88	28.17	15.78
	Mean ± SD	0.75±0.29	0.15±0.05	0.6±0.29	22.11±4.05	14.21±1.74
II (Hunter)	Min	0.7	0.17	0.51	7	9
	Max	0.8	0.19	0.63	22	22
	Mean ± SD	0.74±0.06	0.18±0.01	0.56±0.06	13±7.94	14.33±6.81
IV-A (Morquio)	Min	0.4	0.09	0.21	8.4	13.29
	Max	1	0.21	0.82	40.6	25
	Mean ± SD	0.58±0.23	0.16±0.04	0.4±0.23	19.75±11.14	17.51±4.24
VI (Maroteaux-Lamy)	Min	0.7	0.17	0.51	7	9
	Max	0.8	0.19	0.63	22	22
	Mean ± SD	0.74±0.06	0.18±0.01	0.56±0.06	13±7.94	14.33±6.81
F		0.774	0.39	0.938	1.021	0.548
P		0.53	0.762	0.452	0.418	0.659

F One Way ANOVA test Min = Minimum, Max = Maximum, S.D = Standard Deviation, MPS = Mucopolysaccharidosis. AST = Aspartate aminotransferase, SGOT = Serum Glutamic Oxaloacetic Transaminase ALT = Alanine aminotransferase, SGPT = Serum Glutamic Pyruvic Transaminase
[The normal range; Total bilirubin = 0.25-1.00 mg/dL, Direct bilirubin = 0.00-0.25 mg/dL, Indirect bilirubin = 0.2-0.8 mg/dL, AST = up to 38 U/L, ALT = up to 40 U/L]

DISCUSSION

The clinical characteristics of children and adolescents with different types of MPS involved in the current study were presented in **Table (1**). The IV-A group had the highest average age (11.5 ± 3.78 years), while the VI group had the highest average height (109 ± 9.64 cm), and the II group had the highest average weight (22.33 ± 5.77kg) respectively but without statistically significant difference. The diagnostic age in the Taiwanese children was much lesser as it was recorded to be MPS I, II, IV, and VI, respectively, with **Oguni et al. [4]** median diagnostic ages of 1.5 (MPS I), 3.8 (MPS II), 4.5 (MPS IV) and 3.7 (MPS VI) years, respectively **[4].** While children (3.4-7.1 years) from south and southeastern parts of Turkey were diagnosed with Morquio A syndrome, and had similar length, and body weight to that recorded in the present study**[5]**. It noted worthy to mention that all the patients with MPS types under the study receive ERT.

The mucopolysaccharidoses are genetic disorders of glycosaminoglycans (GAGs) catabolism, that caused by a deficiency in the activity of specific lysosomal enzymes required for GAGs degradation**[6].** In this regard a vast array of enzymes was assayed in the current investigations and the results highly demonstrate that a specific enzyme deficiency was correlated with each type of MPS. As α-iduronidase defect was related to MPS I and it's concentration was 0.25 ± 0.17 micromol/g.prot/ h. Also, Iduronate sulfatase defect was related to MPS II and it's concentration was 0.67 ± 0.58 micromol/l/h. Furthermore, Galactoseamine 6 sulfatase concentration defect (132 ± 76.53 pmol/g.proth/h) was related to MPS IV, and Arylsulfatase-B concentration defect (0.25±0.05 nmol/mg.prot/h) was related to MPS VI. There was statistically significant relation between type of MPS and urinary GACs. On doing Tukey HSD test, the difference was significant between type I and II. Also, the difference was significant between type II and IV-A. On the other hand, type IV-A did not differ from type VI or I**.** In agreement

with the recorded results of the present study, **Valayannopoulos *et al.* [7]** pointed out that MPS VI was associated with a defect in Arylsulfatase. Besides, **Haddley [8]** reported that MPS IV was caused by genetic mutations in N-acetylgalactosamine-6-sulfatase (GALNS) enzyme gene. Furthermore, **Oguni *et al.*[4]** recorded that α-iduronidase defect was specific for MPS I group, and GALNS was specific for MPS IV group. **Tylki-Szymańska [9]** demonstrated that MPS II was associated with a defect in Iduronate sulfatase, and a high accumulation of urinary GAGs.

There was statistically significant relation between type of MPS and presence of mental delay. All patients with type IV-A and VI had no mental delay while all those with type I and II had mental delay. There was statistically non-significant difference between them regarding other clinical manifestations were presented in **Table (3) and cleared in detail in the results**. Similarly, **Regier *et al.* [6]** described the phenotypic features of MPS IV and showed that patients of this group have hip problems (pain and stiffness), visual impairment from corneal clouding, dental abnormalities, and hepatomegaly. Besides, **Tylki-Szymańska[9]** mentioned that MPS II was associated with coarse facial feature, short stature, joint stiffness, skeletal changes, short neck, broad chest, large head circumference, progressive, profound mental retardation, and increased liver and spleen volume. Furthermore, **Melbouci *et al.* [10]** explained that the accumulation of GAGs in MPS patients was the cause of the clinical presentations usually observed such as skeletal dysplasia, bone growth impairment, successive short stature, and growth impairment.

There was statistically non-significant difference between the studied groups with different types of MPS regarding hemoglobin, white blood cells, PCV, MCH, MCHC, or red blood cell count. There was statistically significant difference between the studied groups with different types of MPS regarding platelet count. ,while there was non-significant difference between each two individual groups. There was statistically significant difference between the studied groups with different types of MPS regarding lymphocytic count. , while there was non-significant difference between each two individual groups **(Table 4)**. In agreement with the recorded results in the present study, **Vijayalakshmi [11]** reported normal blood parameters in two Indian children diagnosed as MPS types IV and VI. In addition, **Beck [12]** mentioned that MPS II patients mostly have normal blood parameters. Furthermore, **Jain *et al.* [13]** reported a significant lymphocytosis in a 1½-year-old female child confirmed case of MPS in India. Additionally, **de Melo *et al.*[14]** mentioned that MPS type VI was a rare lysosomal storage disease that presents leukocyte inclusions (Alder-Reilly anomaly) and lymphocytes with metachromatic inclusion surrounded by clear spaces, which was known as Gasser cells.

This study was further extended to investigate the liver function tests among the examined patients of MPS. Interestingly, There was statistically non-significant difference between the studied groups with different types of MPS regarding total, direct bilirubin, AST, ALT, or indirect bilirubin **Table (5)** and detailed in results. These results suggested that liver function tests were not highly specific as a diagnostic feature in MPS diagnosis. This agreed with **Kubaski *et al.*[15]** who mentioned that most MPS types demonstrated an increase in the levels of GAGs in tissues, including blood and urine, however diagnosis was still challenging as specific enzyme assays were still needed for the correct diagnosis.

CONCLUSION

In MPS The accumulation of GAGs in connective tissues of airways led to respiratory system affection Therefore, measurement of such enzymes in combination with different diagnostic tools as the case history, physical features and hematological examination and were essential for correct diagnosis and early interference.

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