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Original Article

OPHTHALMIC MANIFESTATIONS IN PATIENTS WITH MUCOPOLYSACCHARIDOSIS ATTENDING ASSIUT UNIVERSITY CHILDREN HOSPITAL

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Abstract

Background: *Mucopolysaccharidoses (MPSs) are a class of rare lysosomal storage disorders marked by the accumulation of glycosaminoglycans in numerous organs and tissues. These patients frequently experience ocular disorders, including the optic nerve, retina, trabecular meshwork, cornea, and sclera.* ***Objectives:*** *Assessment of the incidence of ophthalmic manifestations in cases with MPSs and the effect of enzymatic replacement on the ophthalmic manifestations among those patients.* ***Methods:*** *All patients under 18 years old with any type of MPSs demonstrated by the enzymatic assay and attended to the Outpatient General Clinics or the Metabolic Unit of Assiut University Children Hospital during the study period were enrolled in the current study. The results of ophthalmologic examinations were recorded, including visual acuity, lens opacity, refractive errors (such as astigmatism, myopia, and hyperopia), and, if feasible, intraocular pressure (IOP) measurement.* ***Results:*** *Among 30 MPSs confirmed patients, 43.3% of those with MPS I, 16.7% with MPS II, 33.3% with MPS IV, and 6.7% with MPS VI. The majority of the studied cases (73.3%) suffered from the error of refraction, mainly hypermetrope, 83.3% had corneal affection, and the ciliary body and iris were affected in almost all studied cases (93.3%). High intraocular pressure was observed in 30.0%, and the eye lens in the form of cataract was affected in ten cases (33.3%). However, the posterior segment was free in all cases except one case that suffered from glaucomatous cupping.* ***Conclusion:*** *Patients with MPS frequently experience ocular problems that result in a marked decline in visual acuity.*

Keywords: *Mucopolysaccharidosis, corneal opacity, visual acuity*

1. Introduction

Mucopolysaccharidoses (MPSs) are a category of illnesses stemming from hereditary deficiencies in lysosomal enzymes, leading to extensive intra- and extracellular buildup of glycosaminoglycans [1,2]. They are categorized based on systemic manifestations and enzyme defects, including MPS IH (Hurler) [3], MPS IS (Scheie), MPS IH/S (Hurler/Sheie), MPS II (Hunter) [4, 5], MPS III (Sanfilippo) [6], MPS IV (Morquio) [7,8], MPS VI (Maroteaux-Lamy) [9], MPS VII (Sly) [10], and MPS IX (Natowicz) [11]. MPSs can cause various systemic symptoms, such as heart abnormalities, intellectual and neurological impairment, skeletal deformities, gastrointestinal problems, respiratory and airway difficulty, and ocular manifestations [1]. Ocular manif-

estations are prevalent in MPSs and can cause profound visual impairment. In addition to retinopathy, optic nerve atrophy and edema, ocular hypertension, and glaucoma, corneal opacification of variable severity is commonly observed [12]. In many cases, new therapeutic options for the systemic aspects of the mucopolysaccharidoses, including enzyme replacement therapy and bone marrow transplantation, have improved prognosis [13]. The main objective of the current study is to assess the incidence of ophthalmic manifestations in patients with MPSs. In addition, it assesses the effect of enzymatic replacement on the ophthalmic manifestations among those patients.

2. Patients and Methods

This hospital-based descriptive cross sectional study was approved by the Regional Ethics Committee at Assiut University (IRB N 17101424). Additionally, informed written consent was given by the participants or their guardians before enrolling in the current research.

2.1. *Patients*

All patients under 18 years old with any type of MPSs confirmed by the enzymatic assay and attending to the Outpatient General Clinics or the Metabolic Unit of Assiut University Children Hospital for receiving enzyme replacement therapy in one year from the 1st of April 2021 up to the end of April 2022 were enrolled in the current study. Patients whose parents refused to participate in the current study were excluded. Specific enzyme activity testing in blood, leukocytes, and/or skin fibroblasts, two-dimensional electrophoresis of urine glycosaminoglycans (GAGs), and/or the discovery of a pathogenic mutation were used to confirm diagnosing MPS [14].

2.2. *Ophthalmologic assessments*

Visual acuity, refractive errors (such as astigmatism, myopia, and hyperopia), lens opacity, and, if feasible, an intraocular pressure (IOP) measurement were among the ophthalmologic tests that were noted. The tests included direct and indirect fundoscopy, slit-lamp examination of the anterior segment, measurement of IOP by pen tonometry, and assessment of best-corrected visual acuity using Snellen charts. Moreover, one observer subjectively rated the degree of corneal opacity as mild (+), moderate (++), or severe (+++). In refractive error assessments utilizing an autorefractor, myopia was characterized by sphere power ≤ -0.50 D, hyperopia by sphere power ≥ 0.50 D, and significant astigmatism by cylinder power ≥ 1.50 D. The IOP readings were categorized as either normal ($\leqq$21 mmHg), ocular hypertension (>21 mmHg) or severe ocular hypertension >30 mmHg [12]. The optic disc's appearance was noted as normal, atrophic, swollen, or cupped visualization, if possible. Through dilated fundal examination via optical coherence tomography (OCT), the presence of retinopathy was identified. It was also used to measure the thickness of the retina and the optic nerve.

2.3. *Statistical analysis*

Statistical analysis was carried out utilizing SPSS (Statistical Package for Social Science; SPSS Inc., Chicago, Illinois, United States) version 22. Data were statistically presented as mean ± standard deviation (±SD), or median and range and compared by Mann Whitney U test or shown as numbers (percentages) and compared by Chi-square ($\chi 2$) test or Fisher Exact test. The P-value was set as significant at the 0.05 level.

3. Results

3.1. *Baseline data*

Table (1) shows that the mean age of the studied patients was 9.40±2.76 years (range: 5-14 years). Out of 30 studied MPS cases, 63.3% were males, and 36.7% were females. The MPS type I was confirmed in 43.3%, MPS type II in 16.7%, MPS

type IV in 33.3%, and MPS type VI in 6.7%. Positive consanguinity and positive family history were documented in 73.3% and 63.3%, respectively. Detailed clinical characteristics of the studied participants are presented in tab. (1). Regarding the eye manifestations of the studied participants, the error of refraction was documented in 70% of the studied cases that suffered from hypermetropia, and one case (3.3%) that suffered from hypermetropia with nystagmus. This result was due to the deposition of GAGs in the cornea, which modifies the corneal curvature, while its deposition in the sclera reduces the axial length which causes hypermetropia. The posterior segment (retina, retinal vessels, macula, fovea, and optic nerve) was free with no abnormalities in 96.6% and only affected in one case (3.3%) that suffered from glaucomatous cupping observed during fundus examination. Anterior segment examination (which composes the pupil, iris, ciliary body, cornea, sclera, and lens) shows the affection of the iris and ciliary body in the form of GAGs deposition in them in 28 cases (93.3%). Corneal affection due to deposition of GAGs in all layers of the cornea that gave ground glass appearance of the cornea during the examination was observed in 19 cases (63.3%), resulting in the diffuse clouding of the cornea in severe form, which was documented in 6 cases (20%). Moreover, deposition of GAGs in the lens (lens affection) was observed in 10 cases (33.3%). IOP was high in nine cases (30%) [borderline for follow-up in one case (3.3%), high for follow-up in 6 cases (20%), and high for treatment in 2 cases (6.7%)]. IOP is affected by an increase in the central thickness of the cornea and its rigidity, so it may falsely increase and needs follow-up in most cases.

Table 1: Baseline data of the 30 studied participants with MPSs

Baseline data	N=30	
Age (years)		
▪ ***Mean ± SD***	9.40 ± 2.76	
▪ ***Median (range)***	9 (5 – 14)	
Sex, n (%)		
▪ ***Male***	19	(63.3)
▪ ***Female***	11	(36.7)
Mucopolysaccharidosis type, n (%)		
▪ ***I***	13	(43.3)
▪ ***II***	5	(16.7)
▪ ***IV***	10	(33.3)
▪ ***VI***	2	(6.7)
Positive consanguinity status, n (%)	22	(73.3)
Positive family history, n (%)	19	(63.3)
Clinical characteristics, n (%)		
▪ ***Coarse facies***	25	(83.3)
▪ ***Joint affection***	29	(96.7)
▪ ***Skeletal affection***	30	(100.0)
▪ ***HSM***	15	(50.0)
▪ ***Abdominal herniation***	16	(53.3)
▪ ***Congenital heart disease***	6	(20)
Delayed mental development, n (%)	9	(30.0)
Delayed motor development, n (%)	13	(43.3)
Eye manifestations		
Error of refraction, n (%)		
▪ ***No error of refraction***	8	(26.7)
▪ ***Hypermetrope***	21	(70.0)
▪ ***Hypermetrope with nystagmus***	1	(3.3)

Posterior segment, n (%)		
▪ ***Free***	30	(100.0)
▪ ***Glaucomatous cupping***	1	(3.3)
Anterior segment, n (%) Iris and ciliary body		
▪ ***Free***	2	(6.7)
▪ ***Affected***	28	(93.3)
Corneal examination		
▪ ***Free***	5	(16.7)
▪ ***Stromal opacity (ground glass appearance)***	19	(63.3)
▪ ***Cloudy***	6	(20.0)
Lens affection		
▪ ***Not affected***	20	(66.7)
▪ ***Affected***	10	(33.3)
Intraocular pressure, n (%)		
▪ ***Normal***	21	(70.0)
▪ ***Borderline for follow-up***	1	(3.3)
▪ ***High for follow-up***	6	(20.0)
▪ ***High for treatment***	2	(6.7)

HSM*: hepatosplenomegaly;* ***Data*** *are presented as mean ± SD and median (range) or number (percentage);* ***P value*** *is significant if <0.05.*

3.2. *Eye manifestations according to MPSs*

The refractive errors, especially hyperm-etropia and corneal affection, prevail in MPS I and II (P=0.009 and 0.018) compared to other MPSs. All patients with MPS type I had normal intraocular pressure compared to 53.8% of the patients with MPS I, 60.0% with MPS II, and 50.0% with MPS VI (P=0.041). Other eye manifestations, such as the examination of the anterior and posterior segments, were comparable between all studied MPS types with the lack of significant differences (P>0.05, for all), tab. (2).

Table 2: Eye manifestations among the 30 studied participants according to the type of MPSs

Eye manifestations	1st, n=13		2nd, n=5				4th, n=5	6th, n=2	P value
Error of refraction									**0.009**
▪ *Normal*	1	(7.7)	0	(0.0)	6	(60.0)	1	(50.0)	
▪ *Abnormal*	12	(92.3)	5	(100.0)	4	(40.0)	1	(50.0)	
Posterior segment									0.233
▪ *Free*	13	(100.0	5	(100.0)	10	(100.0)	2	(100.0)	
▪ *Glaucomatous cupping*	0	(0.0)	1	(20.0)	0	(0.0)	0	(0.0)	
Anterior segment Iris and ciliary body									0.094
▪ *Free*	0	(0.0)	0	(0.0)	1	(10.0)	1	(50.0)	
▪ *Affected*	13	(100)	5	(100.0)	9	(90.0)	1	(50.0)	
Corneal examination									**0.018**
▪ *Free*	0	(0.0)	0	(0.0)	4	(40.0)	1	(50.0)	
▪ *Affected*	13	(100)	5	(100.0)	6	(60.0)	1	(50.0)	
Lens affection									0.472
▪ *Not affected*	10	(76.9)	4	(80.0)	5	(50.0)	1	(50.0)	
▪ *Affected*	3	(23.1)	1	(20.0)	5	(50.0)	1	(50.0)	
Intraocular pressure									**0.041**
▪ *Normal*	7	(53.8)	3	(60.0)	10	(100)	1	(50.0)	
▪ *High*	6	(46.2)	2	(40.0)	0	(0.0)	1	(50.0)	

Data are shown as numbers (percentages). Statistically significant at p < 0.05.

3.3. *Eye manifestations according to patient's age:*

No significant differences were found between the MPS types, except for lens affection, which was more prevalent among older children (13.3% versus 53.3%, P=0.020) in the included groups, respectively tab. (3).

Table 3: Eye manifestations among the 30 participants according to the type of MPSs

Eye manifestations	< 9 years (n=15)		≥ 9 years (n=15)		P value
Error of refraction					1
▪ ***Normal***	4	(26.7)	4	(26.7)	
▪ ***Abnormal***	11	(73.3)	11	(73.3)	
Posterior segment					----
▪ ***Free***	15	(100.0)	15	(100.0)	
▪ ***Glaucomatous cupping***	0	(0.0)	1	(6.7)	
Anterior segment Iris and ciliary body					0.483
▪ ***Free***	2	(13.3)	0	(0.0)	
▪ ***Affected***	13	(86.7)	15	(100.0)	
Corneal examination					1
▪ ***Free***	2	(13.3)	3	(20.0)	
▪ ***Affected***	13	(86.7)	12	(80.0)	
Lens affection					0.020
▪ ***Not affected***	13	(86.7)	7	(46.7)	
▪ ***Affected***	2	(13.3)	8	(53.3)	
Intraocular pressure					1
▪ ***Normal***	10	(66.7)	11	(73.3)	
▪ ***High***	5	(33.3)	4	(26.7)	

Numbers (percentages) are used to represent data. Statistically significant at $p < 0.05$.

3.4. *Association between the eye manifestations and duration of enzymatic replacement therapy*

Table (4) shows no significant association between the eye manifestations and the duration of enzymatic replacement therapy among the studied cases.

Table 4: Association between the eye manifestations and the duration of enzymatic replacement therapy among the 30 studied MPCSs participants

Eye manifestations		Median duration of enzymatic replacement therapy	P value
Error of refraction	Normal	2.5 (1 – 5)	0.504
	Abnormal	2 (0 – 10)	
Anterior segment Iris and ciliary body	Free	2 (1 – 3)	0.901
	Affected	2 (0 – 10)	
Cornea	Free	3 (1 – 4)	0.746
	Affected	2 (0 – 10)	
Lens	Free	2 (0 – 10)	0.880
	Affected	2.5 (1-5)	
Fundus examination	Free	2 (0 – 6)	0.067
	Glaucomatous cupping	10	
Intraocular pressure	Normal	2 (0 – 6)	0.056
	High	1 (0 – 10)	

Median (range) is the form of data representation. Statistically significant at $p < 0.05$.

4. Discussion

The present study was a hospital-based observational cross-sectional trial aimed to evaluate the incidence of different ophthalmic manifestations in the various types of MPS disorders in patients attending Assiut University Children Hospital. It included 30 pediatric patients with confirmed MPS, with a mean age of 9.40± 2.76 years (range; 5-14 years). Agreeing with the present study, the Asian retrospective study of Lin et al. on 129 patients with MPS reported that the mean age of the studied cases was 9.1±5.3 years (range; 0.7-19.5 years) [15]. Similarly, Tulebayeva et al. stated that at the time of diagnosis, the mean age of the observed

patients was 10.6 years (range 5-18 years) [16]. A younger mean age was reported by the Egyptian study of El Falaki et al., who found that the median age at examination was 2.3 years and ranged from 1 to 9 [17]. This difference was attributed to the difference in the inclusion criteria, as the authors enrolled only younger-aged children. Our studied cases were predominantly males. Out of the 30 studied MPS cases, 19 cases (63.3%) were males, and 11 cases (36.7%) were females, with a male-to-female ratio of 1.7:1. In line with the current study, El Falaki et al. reported a higher male-female ratio of 4:1. Similarly, Lin et al. found a higher male-female ratio of 2.2:1 than observed by the current study. This finding could be because the higher male-to-female ratio may be common in Arab countries because they are more interested in males [18]. Additionally, MPS disorders are known to be autosomal recessive disorders, except for MPS II (Hunter syndrome), which has X-linked inheritance and mainly affects males [19]. Researchers noted that different geographic areas and/or ethnic backgrounds have different prevalence rates of MPS for each subtype. A broad variety of mutations, mainly missense mutations, cause each type of MPS [20]. In Egypt, a study by El Falaki et al. reported that Hurler syndrome was the most prevalent MPS type, followed by Sanfillipo, then Morquio, and last, Hunter MPS [17]. A similar finding was reported by Selim et al. (2016), who reported that MPS I was the highest MPS type, followed by MPS IV, then MPS VI, and last MPS III [21]. A somewhat similar finding was reported in the current study as we observed that MPS I had the highest prevalence (43.3%), followed by MPS IV (33.3%), then MPS II (16.7%), and MPS VI (6.7%). Meanwhile, no one had MPS III. In contrast to the current study, the Egyptian study by Fateen et al. revealed that out of 1,448 suspected cases, 42.9% of MPS patients were diagnosed, revealing that MPS III was the highest type, followed by MPS I and MPS IVA [18]. Positive consanguinity and a positive family history of similar disease were documented in 73.3% and 63.3%, respectively. This finding was higher than that reported by the Egyptian study of El Falaki et al., who reported consanguinity in 53.3% and a similar family condition in 40% of cases [17]. It was also higher than the similar family condition reported by Selim et al. in 38.0% [21]. in spite of this high prevalence of consanguinity and positive family of similar disease for such lysosomal disorders. Genetic testing for various metabolic illnesses is currently not a standard procedure in the Egyptian healthcare system, is not covered by insurance, and is too costly for individual families. Specific GAG(s) are deposited in various cells, tissues, and organs depending on the enzyme deficit. This might have complex clinical effects ranging from the involvement of the central nervous system to multi-organ failure [22]. These deposits change the ultrastructure of the tissue and the morphology of the cells, which leads to a progressive physiological failure that manifests clinically early and can eventually end in blindness or visual impairment. Typical coarse facial characteristics, growth retardation, skeletal deformities, respiratory difficulties, cardiac valvular abnormalities, gastrointestinal problems, and intellecttual and behavioral impairment are caused by the accumulation of GAGs in various organs [23]. This explains the current finding, as we observed that 83.3 % had coarse facies with prominent foreheads, depressed nasal bridges, enlarged mouths, and thick lips. Joint affection in the form of "joint contracture and rigidity observed in wrist, ankle and knees" and joint instability as hypermobility of metacarpal joints were all observed in almost all cases (96.7%). Skeletal affection "inappropriate short stature, short stature with long limbs, abnormal bone size, e.g., broad wrists and increased head circumference, kyphoscoliosis, pigeon shaped chest, and prominent maxilla" was reported in all

cases (100%). According to abdominal examination, hepatosplenomegaly was documented in 50%, and abdominal herniation in 53.3%. In addition, congenital heart disease was documented in six cases (four cases (13.3%) with mitral regurgitation, and one case (3.3%) with mitral prolapse, another case (3.3%) with aortic regurgitation). Delayed mental development, e.g., significant lag in achieving age-appropriate developmental milestones, social and emotional skills, cognition, and language and speech, was observed in 9 cases (30%). Delayed physical development for fine and gross motor skills, e.g., sitting, standing, walking, jumping, and running, was documented in 13 cases (43.3%). Moreover, the mechanism of growth impairment and short stature in various MPS types can result from the growth plate defects, such as GAG deposition in bone and cartilage, impaired osteoblast function, the growth plate's disorganized structure, hypertrophic chondrocytes, and decreased matrix deposition. Other organs can continue to grow normally in comparison to the skeletal system's growth retardation, resulting in an imbalance in growth manifestations, such as hepatosplenomegaly, tracheal obstruction, a prominent forehead, spinal cord compression, and dwarfism with a short neck and short trunk [15]. While most MPS children seem normal at birth, as they become older, they may exhibit a variety of clinical symptoms, including severe developmental limitations. The age at onset and the growth rate vary for each type of MPS. As a result, growth assessment is essential for assessing the effectiveness of treatments and disease progression. In the current study, 22/30 cases (73.3%) suffered from the error of refraction, mainly hypermetrope. In the anterior segment, the iris and ciliary body were affected in almost all studied cases (93.3%). Also, the majority of the studied cases had corneal affection (83.3%) in the form of (63.3% had stromal opacity and ground glass appearance, and 20.0% had cloudy cornea). Corneal clouding is caused by the accumulation of yellowish-grey granules consisting of GAGs deposited in all corneal layers, as well as the displacement of collagen fibrils in the stroma. Excess accumulation of GAG in the cornea influences keratocyte dimensions and disturbs the orderly arrangement of collagen fibrils in the stroma, resulting in corneal clouding [24]. In this study, the eye lens was affected in the form of stromal opacity, which was observed during examination due to GAGs deposition in ten cases (33.3%). Additionally, high IOP was observed in 30.0%. However, the posterior segment was free in all cases except one case (3.3%) that suffered from glaucomatous cupping, which was observed during fundus examination. This finding should be interpreted with caution as the corneal clouding could prevent an accurate fundus examination. On comparing the eye manifestations of the studied patients according to the MPS types, we observed that refractive errors, particularly hypermetropia, were common in MPS I and II. This finding was in line with previous literature [25]. It could be because of the inflexible corneal curvature and the inelastic shortened axial length of the sclera, all of which relate to GAG storage [26]. Corneal affection, such as opacity and clouding, was also common in cases having either MPS type I and II in comparison with other groups. The literature demonstrated that corneal clouding is more common in MPS type I [10,24]. Consistent with the current study, Selim et al. observed that corneal clouding was seen in MPS types I and II patients but was absent in other MPS types [21]. This corneal clouding may make it difficult to see the optic nerve and corneal-scleral angles clearly, which are essential for diagnosing glaucoma. Therefore, monitoring IOP is a valuable technique for diagnosing and monitoring glaucoma. Additionally, changes in corneal thickness may affect IOP measurements [27]. In the present

study, we observed that all patients with MPS type IV had normal intraocular pressure compared to 53.8% of patients with MPS type I, 60.0% with MPS type II, and 50.0% with MPS type VI (P= 0.041). On the other hand, because of the increased corneal stiffness, MPS cases might have falsely raised IOP. The corneal layers, optic nerve, photoreceptor layers, and retinal nerve fiber layers (RNFL) could all be seen with the aid of optical coherence tomography (OCT). IOP can be measured more accurately with Goldmann applanation tonometry and the ocular response analyzer since they depend less on corneal characteristics [28,29]. Consequently, ophthalmologists must diagnose glaucoma in MPS patients with extreme caution, taking into account the possibility that the measured IOP reading is inaccurate. Meanwhile, other eye manifestations, such as anterior and posterior segment examination, were comparable between all studied MPS types with no significant difference. Another interesting finding of the current study was that older patients ≥9 years old suffered from lens affection more commonly than younger patients (<9 years). It is well known that children with several clinical symptoms, e.g., significant growth and multi-organ impairments with age [15], this could explain our findings. Hematopoietic stem cell transplantation and enzyme replacement therapy are the primary treatments for MPS disorder [30]. While these therapies cannot reverse the course of the diseases, they can slow down or stop their advancement. Understanding the growth pattern and natural history of MPS is crucial for determining the effectiveness of treatment [15]. In the current study, we observed borderline significance between the increased intraocular pressure and shorter duration of enzymatic replacement therapy (P=0.056). Thus, ERT could help minimize disease progression. However, further trials should be conducted to evaluate the role of ERT accurately on eye manifestations in patients with MPS because the current study was only a descriptive cross-sectional study.

5. Conclusion

Patients with MPS frequently experience ocular problems that result in a marked decline in visual acuity. Refractive errors, especially hypermetropia, and corneal involvement "in form stromal opacity +/- clouding" were common in cases with MPS I & Ⅱ in comparison with other groups. IOP was not elevated in patients with MPS type Ⅳ compared to 53.8% with MPS Ⅰ, 60.0% with MPS Ⅱ, and 50.0% with MPS Ⅵ. Further, larger case-controlled trials should be conducted to evaluate the role of ERT accurately on eye manifestations in MPS patients.

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