Med. čas. 2023; 57(4): 131-135.
ORIGINALNI NAUČNI ČLANAK
doi: 10.5937/mckg57-43937
COBISS . SR - ID 141279753
UDK. 616-008.9-056.7-085 617.7-085-053.2

OCULAR MANAGEMENT OF MUCOPOLYSACCHARIDOSIS (MPS)

Azzam A. Ahmed, Muna M. Ahmed
University of Mosul, College of Medicine, Mosul, Iraq

ЛЕЧЕЊЕ МУКОПОЛИСАХАРИДОЗЕ

Азам А. Ахмед, Муна М. Ахмед
Универзитет у Мосулу, Медицински факултет, Мосул, Ирак

ABSTRACT

Objectives. Mucopolysaccharidoses (MPS) are a collection of rare ailments of storage lysosomes distinguished by the aggregation of glycosaminoglycans (GAGs) at distinct regions of the eye. Follow-up is necessary to enable the right direction for the subsequent therapy. The objective of this research is to define the clinical presentation and treatment modalities in MPS patients.

Methods. A total of 16 children diagnosed with MPS were followed-up for 10 years. All cases in this study underwent cycloplegic refraction using 1% cyclopentolate (API) and streak retinoscope (Keeler).

Results. The findings confirmed that all patients (100%) presented with corneal cloudiness, half of them (50%) were diagnosed as having glaucoma and just above a third of children (37.5%) suffer from retinopathy.

Conclusion. Early detection and diagnosis are crucial to protect the visual function, and experience at different levels is required for reaching the correct diagnosis.

Key words: *mucopolysaccharidoses; glycosaminoglycans; eye.*

САЖЕТАК

Циљ. Мукополисахаридозе (МПС) јесу ретке болести ускладиштених лизозома, које се разликују по агрегацији гликозаминогликана (ГАГ) у различитим регионима ока. Праћење је неопходно да би се омогућио прави избор терапије. Циљ овог истраживања било је дефинисање клиничке слике и начина лечења пацијената са МПС.

Методе. Праћено је укупно 16 деце са дијагнозом МПС 10 година. Сви случајеви у овој студији подвргнути су циклоплегичној рефракцији коришћењем 1% циклопентолата (АПИ) и ретиноскопа у облику трака (Keeler).

Резултати. Налази су потврдили да су сви пацијенти (100%) имали замућење рожњаче, половина њих (50%) имала је дијагнозу глаукома, а нешто више од трећине деце (37,5%) пати од ретинопатије.

Закључак. Рано откривање и дијагноза од кључне су важности за заштиту визуелне функције, а за постављање тачне дијагнозе потребно је искуство на различитим нивоима.

Кључне речи: *мукополисахаридозе, гликозаминогликани, око*

INTRODUCTION

Ocular issues in mucopolysaccharidoses (MPS) are very rare, with a variety of representations regarding the time of presentation and severity (1-5). It is the build-up of glycosaminoglycan (GAG) that causes ocular manifestations. This accumulation may affect the eye structures (sclera, cornea, trabecular meshwork, and retina), optic nerve, and even the posterior visual pathways)2,3(. Amblyopia, squint, and refractive errors are very common among those involved with these metabolic problems, necessitating satisfactory rectification for better development of vision (3). Early detection is the key to the prognosis profile (6). The children affected by this problem are often diagnosed late. The eye doctor orchestrates a pivotal role in early detection as well as management. The ocular presentation is existing in all kinds of mucopolysaccharidosis (MPS), in particular type I, IV and VII (7).

The opacification of the cornea is due to the deposition of yellowish-greyish spherules which consist of glycosaminoglycan (GAG) which is settled in stromal lamellae of the cornea, impacting keratocytes and disrupting the arrangement of corneal fibrils, causing corneal cloudiness. Excessive GAG stockpile in the cornea impacts keratocyte size and corrupts the stromal collagen fibrils' geometrical construct, leading to the cloudiness of the cornea (2). Corneal clouding is characterized by being slowly progressive and diffuse, from white- to white, with eventual visual loss (3,4). Sometimes a dense corneal opacity does not enable the ophthalmologist to inspect the crystalline lens and posterior segment structures. In line with the recorded literature, the corneal clouding is more frequent in MPS 1H. Clearing of the cornea is rare, despite the availability of enzyme replacement therapy (ERT). This is especially true if this therapy is initiated in a well-established disease. The vast majority of records claim stabilizing impact of ERT on corneal opacity and visual acuity (2).

GAG tend to deposit in the trabecula sites with subsequent intraocular pressure elevation and probable development of open-angle glaucoma and narrow-angle glaucoma. (8, 9). Those who are known to have MPS I and MPS VI are more likely known to have glaucoma as the disease progresses (8-12). The majority of abnormalities can be shown using goniolens for iridocorneal angle (6). The slit-lamp stigmata of glaucoma encompasses optic nerve enlargement, the elevation of IOP and visual field defect, which, if not detected early, might step forward

Primljen/Received: 11.04.2023.
Prihvaćen/Accepted: 17.02.2024.

Dr. Azzam Abdul-Kader Ahmed
Mosul College of Medicine
University of Mosul, 41001 Mosul, Ninavaha, Iraq
Phone: +964 771 214 531 1
E-mail: azzamabdahm@uomosul.edu.iq

doi: 10.5937/mckg57-43937
COBISS . SR - ID 141279753
UDK. 616-008.9-056.7-085 617.7-085-053.2

leading to irreversible loss of vision. Visual acuity can occur due to damage to the optic nerve, which happens especially in people with glaucoma, a condition where the optic nerve is damaged due to increased pressure in the eye. It's important to note that the earlier glaucoma onsets, the more severe the impact on vision is. So, it is crucial to seek regular eye check-ups to catch any issues early on and offer the proper treatment.

The build-up of GAGs within retinal pigment epithelial cells (RPE) has a devastating effect on photoreceptor cells, leading to a significant loss in visual function. This process intensifies over time, causing further damage and deterioration (13,14). Optic atrophy may happen with associated retinal degeneration which manifests as night blindness (15). The right maturation of visual function can be hampered and accompanied by a variety of refractive errors, but it is mainly due to mixed hyperopic astigmatism (3, 4).

PATIENTS AND METHODS

A sample of 16 children who had been diagnosed with MPS was followed-up for the last ten years (from October 2010 till the end of December 2020 at the author clinic) in collaboration with the pediatric department at Medical City in Bagdad.

Eye assessment is done by one ophthalmologist (author). Possible visual acuity was evaluated using Kay pictures in preverbal children and E-game for those who are school-age. The assessment also includes slit-lamp biomicroscopy, which allows the valuation of corneal clarity, anterior chamber depth, pupillary light reactions, relative afferent pupillary defect (RAPD) and transparency of the crystalline lens, corneal clouding can hamper fundus visualization influencing the follow-up pathological development in the retina and optic disc. Assessment of binocular single vision and ocular muscle misalignment in children include both motor and sensory component evaluation of squint. All cases in this study underwent cycloplegic refraction using 1% cyclopentolate (API) and streak retinoscope (Keeler). Some cases with severe corneal cloudiness might render their evaluation a hard task. All children were scheduled for examination under anaesthesia (EUA) for a comprehensive evaluation and thorough ocular examination. This examination includes dilated ophthalmoscopic examination, using an indirect ophthalmoscope, cyclo-refraction with streak retinoscope, corneal diameter measurement, IOP measurement, B-scan ultrasonography and biometry. In terms of visual field testing, and due to some intellectual impairment of those patients: the ophthalmologist confronted the child drawing their attention centrally and then, coloured lighting toys were beginning to move from the field periphery toward the centre. A child with an average visual field will attempt to follow the toy or there is saccadic movement and the test repeated in other field quadrants.

RESULTS

Sixteen children were enrolled in this follow-up study, seven males and nine females. Their age range was between 4-11 years. In terms of refractive errors, the majority (66.7%) were having hyperopic astigmatism which was more prominent at ages 5-7. Myopic astigmatism was lower in presentation (25%) and only two children (8.3%) were surprisingly emmetropic (Table 1, Figure 1).

Regarding the treatment modality (Figure 2); while glaucoma surgery in the form of trabeculectomy, using Harms trbeculotomes, was the most frequent surgical procedure, full-thickness corneal graft surgery and intravenous enzyme infusion share nearly equal proportions.

There was a diversity of presentation in those children (Figure 3), and, unfortunately, all forms negatively impacted visual acuity. All patients (100%) presented with corneal cloudiness, half of them (50%) were diagnosed as having glaucoma and just above a third of children (37.5%) suffer from retinopathy. The last presentation was those with optic nerve abnormalities or another less frequent form such as iris coloboma with 25% for the former and only 20.8% for the latter.

DISCUSSION

The possible management of ocular MPS might include multidisciplinary approaches:

Dispensing Glasses: Hyperopic astigmatism was the most common form of refractive error among those children. Utilizing streak retinoscopy and, if possible, auto-refractometer to prescribe the appropriate glasses (16-21). In our patients, we detected such errors (Table 1), and the alliance with the optometrist for photochromatic lens dispersion helped lower troublesome photophobia. By undergoing an examination with cycloplegia, patients can ensure that their spectacles are tailored to their specific condition (2, 22). Despite this action, some children may not gain the advantages of wearing glasses due to partial or complete amblyopia. Therefore, orthoptic therapy with part-time or full-time occlusion is done depending on the severity of visual affection.

Topical lubricants: the dry eye is also common among those children due to keratoconjunctivitis sicca (23) and for those topical lubricant drops in form of methylcellulose were prescribed.

Antiglaucoma therapy: For those with high and consistent IOP elevation, a topical beta blocker is the drug

doi: 10.5937/mckg57-43937
COBISS . SR - ID 141279753
UDK. 616-008.9-056.7-085 617.7-085-053.2

Table 1. Demographics of study sample.

Variable	Hyperopic astigmatism (n=16)	Myopic astigmatism (n=6)	Emmetropia (n=2)	Total (n=24)
	No. (%)	No. (%)	No. (%)	No. (%)
Age (years)				
4	2 (12.5)	0 (0.0)	0 (0.0)	2 (8.3)
5	5 (31.3)	2 (33.3)	2 (100.0)	9 (37.5)
6	4 (25.0)	1 (16.7)	0 (0.0)	5 (20.8)
7	2 (12.5)	1 (16.7)	0 (0.0)	3 (12.5)
8	1 (6.3)	1 (16.7)	0 (0.0)	2 (8.3)
9	1 (6.3)	1 (16.7)	0 (0.0)	2 (8.3)
11	1 (6.3)	0 (0.0)	0 (0.0)	1 (4.2)
Sex				
Male	7 (43.8)	0 (0.0)	2 (100.0)	9 (37.5)
Female	9 (56.3)	6 (100.0)	0 (0.0)	15 (62.5)

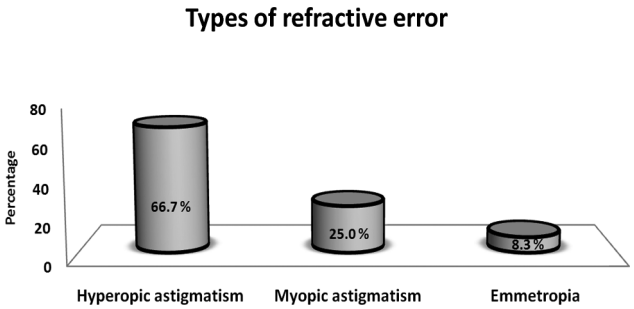

Figure 1. Distribution of study sample according to the type of refractive error

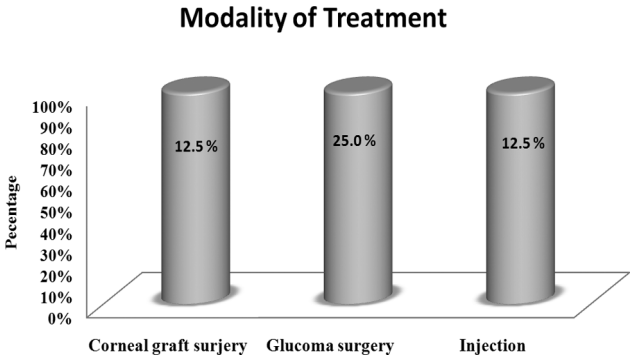

Figure 2. Distribution of study sample according to the modality of treatment

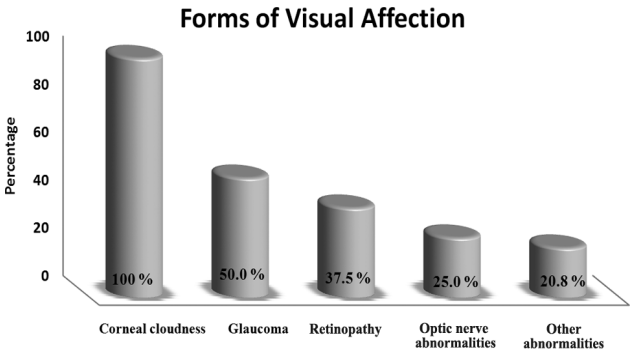

Figure 3. Distribution of study sample according to forms of visual affection.

of choice 2 was initiated (timolol 0.5% API) for controlling the IOP. For those who are not brought under control, a trabeculectomy surgery was planned and scheduled.

Enzyme infusion therapy: NAGLAZYME for type VI (MPS VI)

This drug has initial U.S. approval from 2005. It is administered as an intravenous infusion. The vial comes as 5 mg per 5 ml and needs to be diluted with normal saline (0.9% sodium chloride) before administration. This enzyme therapy aims to provide an exogenous source of the enzyme to be consumed by lysosomes, increasing the catabolism of GAG. The treatment is given as 1 mg/ kg body weight ideally once-weekly intravenous infusion. This vial comes as a sterile, nonpyrogenic, colourless to pale yellow, clear to the slightly opalescent solution. There is no known contraindication for such therapy, however, there are certain precautions which include anaphylaxis, allergic reactions, and the risk of cardiopulmonary failure. Trained medical staff with appropriate medical facilities and equipment can mitigate such adverse reactions.

Corneal Surgery: severe corneal cloudiness which is a potential risk for amblyopia. Those children were referred to a corneal surgeon for full-thickness corneal graft and followed up regularly for graft stability. Refraction and selective suture removal one-year post-grafting. (24) Corneal graft surgery is proposed when corneal opacity is so severe that precludes visual acuity testing and posterior segment assessment as well as in those whose visual acuity is below 0.3.

The current choice of dealing with corneal cloudiness has always been full-thickness corneal grafting. However, a new trend has recentyly initiated by many corneal surgeons (25-28), preferring deep anterior lamellar keratoplasty (DALK) in such a scenario, as the child's endothelium is preserved hence avoiding the chance of endothelial layer rejection. Furthermore, such an approach

doi: 10.5937/mckg57-43937
COBISS . SR - ID 141279753
UDK. 616-008.9-056.7-085 617.7-085-053.2

appears to provide more resilient corneal tissue against any future injury years following the operation. In addition, it seems that the presence of Descemet's membrane in DALK surgery creates a bitof a challenge when it comes to preventing the accumulation of GAG. This build-up of GAG can ultimately result in the reappearance of cloudiness in the transplanted cornea.

In a ground-breaking study, investigators from both Europe and America, studies 32 patients who underwent a comprehensive evaluation of their keratoplasty procedures. The results were astounding: while only three patients received a deep anterior lamellar keratoplasty, a whopping 45 patients underwent a full-thickness graft. After their follow-up visits, a remarkable 63% of patients experienced a favorable outcome in their first eye. This is a promising indication that keratoplasty is becoming increasingly effective in restoring vision and improving the quality of life for those who need it most (28). Corneal graft rejection occasions happened in twenty-three percent. At the conclusive follow-up visit, an incredible number (94%) of patients demonstrated a crystal clear graft, taking into consideration that the mean follow-up time was 70 months, with some patients being monitored for up to 186 months.

Glaucoma Surgery: As most of the attending children with MPS had corneal cloudiness, trabeculotomy with Harms trbeculotomes was performed with close follow-up of the intraocular pressure post-operatively together with optic nerve evaluation if the visibility enabled this examination.

In conclusion, ocular MPS have corneal, retinal and optic nerve involvement as well as other less frequent presentation. Early diagnosis and annual follow-ups are crucial. Such conditions require teamwork at different levels. Due to behavioural challenges in those cases, examination under anaesthesia is considered the main pillar of ocular assessment which dictates the subsequent modality of treatment aiming to enhance the quality of vision and hence the quality of life.

REFERENCES

1. Kottler U, Demir D, Schmidtmann I, Beck M, Pitz S. Central corneal thickness in mucopolysaccharidosis II and VI. Cornea 2010; 29: 260–2.
2. Fahnehjelm KT, Ashworth JL, Pitz S, et al. Clinical guidelines for diagnosing and managing ocular manifestations in children with mucopolysaccharidosis. Acta Ophthalmol 2012; 90: 595-602.
3. Ashworth JL, Biswas S, Wraith E, Loyd IC. The ocular features of the mucopolysaccharidoses. Eye 2006; 20: 553–63.
4. Ashworth JL, Kruse FE, Bachmann B, et al. Ocular manifestation in the mucopolysaccharidoses - review. Clin Exp Ophthalmol 2010; 28: 12–22.
5. Alroy J, Haskins M, Birk DE. Altered corneal stromal matrix organization is associated with mucopolysaccharidosis I, III and VI. Exp Eye Res. 1999; 68:523–30.
6. Summers CG, Ashworth JL. Ocular manifestations as key features for diagnosing mucopolysaccharidoses. Rheumatology 2011; 50: v34–40.
7. Cantor LB, Disseler JA, Wilson FM 2nd. Glaucoma is the Maroteaux-Lamy syndrome. Am Ophthalmol 1989; 108: 426–30.
8. Nowaczyk MJ, Clarke JT, Morin JD. Glaucoma as an early complication of Hurler's disease. Arch Dis Child 1988; 63: 1091–3.
9. Spellacy E, Bankes JL, Crow J, Dourmashkin R, Shah D, Watts RWE. Glaucoma in a case of hurler disease. Br J Ophthalmol 1980; 64: 773–8.
10. Quigley HA, Maumenee AE, Stark WJ. Acute glaucoma in systemic mucopolysaccharidosis I-S. Am J Ophthalmol 1975; 80: 70–2.
11. Mullaney P, Awad AH, Millar L. Glaucoma in mucopolysaccharidosis 1-H/S. J Pediatr Ophthalmol Strabismus 1996; 33: 127–31.
12. Mack HG, Symons RCA, de Jong G. Bull's eye maculopathy and subfoveal deposition in two mucopolysaccharidosis type I patients on long-term enzyme replacement therapy. Am J Ophthalmol Case Rep 2017; 9: 1–6.
13. Collins ML, Traboulsi EI, Maumenee IH. Optic nerve head swelling and optic atrophy in the systemic mucopolysaccharidoses. Ophthalmol 1990; 97: 1445–9.
14. Ashworth JL, Biswas S, Wraith E, Lloyd IC. Mucopolysaccharidoses and the eye. Surv Ophthalmol 2006; 51: 1–17.
15. Bradbury JA, Martin L, Strachan IM. Acquired Brown's syndrome associated with hurler-Scheie's syndrome. Br J Ophthalmol 1989; 73: 305–8.
16. Ferrari S, Ponzin D, Ashworth JL, et al. Diagnosis and management of ophthalmological features in patients with mucopolysaccharidoses. Br J Ophthalmol 2011; 95: 613–9.
17. Javed A, Aslam T, Jones SA, Ashworth J. Objective quantification of changes in corneal clouding over time in patients with mucopolysaccharidoses. Invest Ophthalmol Vis Sci 2017; 58: 954–8.
18. Javed A, Aslam T, Ashworth J. Use of new imaging in detecting and monitoring ocular manifestations of the mucopolysaccharidoses. ACTA Ophthalmol 2016; 94: e-676–82.

doi: 10.5937/mckg57-43937
COBISS . SR - ID 141279753
UDK. 616-008.9-056.7-085 617.7-085-053.2

19. Fahnehjelm KT, Chen E, Winiarski J. Corneal hysteresis in mucopolysaccharidosis I and IV. Acta Ophthalmol 2012; 90: 445–8.
20. Martin LM, Nilsson AL. Rarebit perimetry and optic disk topography in pediatric glaucoma. J Pediatr Ophthalmol Strabismus 2007; 44: 223–31.
21. Flaherty M, Geering K, Crofts S, Grigg J. Ocular and electrophysiological findings in a patient with sly syndrome. Ophthalmic Genet 2017; 38: 376–9.
22. Fahnehjelm KT, Tornquist AL, Winiarski J. Ocular axial length and corneal refraction in children with mucopolysaccharidosis (MPS I-Hurler). Acta Ophthalmol 2012; 90: 287–90.
23. Fahnehjelm KT, Tornquist AL, Winiarski J. Dry-eye syndrome after allogenic stem-cells transplantation in children. Acta Ophthalmol 2008; 86: 253–8.
24. Fenzl CR, Teramoto K, Moshirfar M. Ocular manifestations and management recommendations of lysosomal storage disorders I: mucopolysaccharidoses. Clin Ophthalmol 2015; 9: 1633–44.
25. Harding SA, Nischal KK, Upponi-Patil A, Fowler DJ. Indications and outcomes of deep anterior lamellar keratoplasty in children. Ophthalmol 2010; 117: 2191–5.
26. Rahmati-Kamel M, Javadi M, Shojaei A, Eslani M, Karimian F. Deep anterior lamellar keratoplasty for Maroteaux-Lamy syndrome. Cornea 2010; 29: 1459–61.
27. Ganesh A, Bruwer Z, Al-Thihli K. An update on ocular involvement in mucopolysaccharidoses. Curr Opin Ophthalmol 2013; 24: 379–88.
28. Pinello L, Busin M, Fontana L, Dua HS. Application of (lamellar) keratoplasty and limbal stem cell transplantation for corneal clouding in the mucopolysaccharidoses—a review. Clin Exp Ophthalmol 2010; 38(Suppl): 52–62.