

REVIEW

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# Glaucoma in mucopolysaccharidoses

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## Abstract

Mucopolysaccharidoses are a group of lysosomal storage disorders that are caused by deficiency of enzymes involved in glycosaminoglycans degradation. Due to low prevalence and high childhood mortality, researches on mucopolysaccharidoses were mainly focused on the fatal manifestations. With the development of treatments, more and more mucopolysaccharidoses patients were treated by approved therapies, thereby getting prolonged life span and improved quality of life. Abnormal accumulation of glycosaminoglycans in the eye may block trabecular meshwork, thicken sclera and change mechanical behavior of lamina cribrosa, which, by increasing intraocular pressure and damaging optic nerve, could cause glaucoma. Glaucoma was the leading cause of irreversible blindness worldwide, but it was rarely reported in mucopolysaccharidoses patients. Although non-fatal, it seriously affected quality of life. Prevalence of glaucoma in mucopolysaccharidoses patients (ranged from 2.1 to 12.5%) indicated that glaucoma in patients with mucopolysaccharidoses was worthy of attention and further study, thereby improving the quality of life for MPSs patients.

**Keywords:** Mucopolysaccharidoses, Mucopolysaccharidosis, Glaucoma, Glycosaminoglycans, Rare disease, Lysosomal storage disorders

## Background

Mucopolysaccharidoses (MPSs) are rare lysosomal storage disorders that are caused by abnormal accumulation of glycosaminoglycans (GAGs), which is due to deficiency of enzymes involved in degradation of GAGs [1]. MPSs are classified into seven subtypes. Six subtypes of MPSs (type I, III, IV, VI, VII and IX) are inherited in an autosomal recessive manner, while mucopolysaccharidosis (MPS) II is X-linked [2]. Milder forms of MPS I and II, MPS IV, and MPS VI are not considered to be progressive or neuronopathic, although patients may function abnormally in neurocognitive ability and/or behavior [3].

Due to low prevalence and high childhood mortality of MPSs, researches were mainly focused on the fatal manifestations. Governments typically stimulated

development of specific therapies for MPSs by providing regulatory and economic incentives. For example, enzyme replacement therapies for non-neuronopathic forms of MPS I and II have been developed and approved to date [4]. Life span and quality of life were improved after the treatment [5, 6]. Non-fatal manifestations of patients with MPSs, i.e. ocular manifestations, should be noticed and intervened earlier to get better prognosis. Ophthalmological findings (corneal clouding, glaucoma, optic neuropathies, and retinopathies) were common and variable in MPSs and might result in significant visual impairment [1, 7].

Glaucoma, as a leading cause of irreversible blindness, is a group of eye conditions that are characterized by progressive degeneration of retinal ganglion cells [8, 9]. Glaucoma was untreatable, but the rate of visual field deterioration could be slowed down by reducing intraocular pressure (IOP) [10]. Prevalence of glaucoma in MPSs patients (ranged from 2.1% to 12.5%) suggested that glaucoma in patients with MPSs was worthy of attention [11]. This review was published to attract more attention from people about glaucoma in patients with MPSs and aimed

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to increase efforts in improving the quality of life for MPSs patients.

**Glaucoma in MPSs**

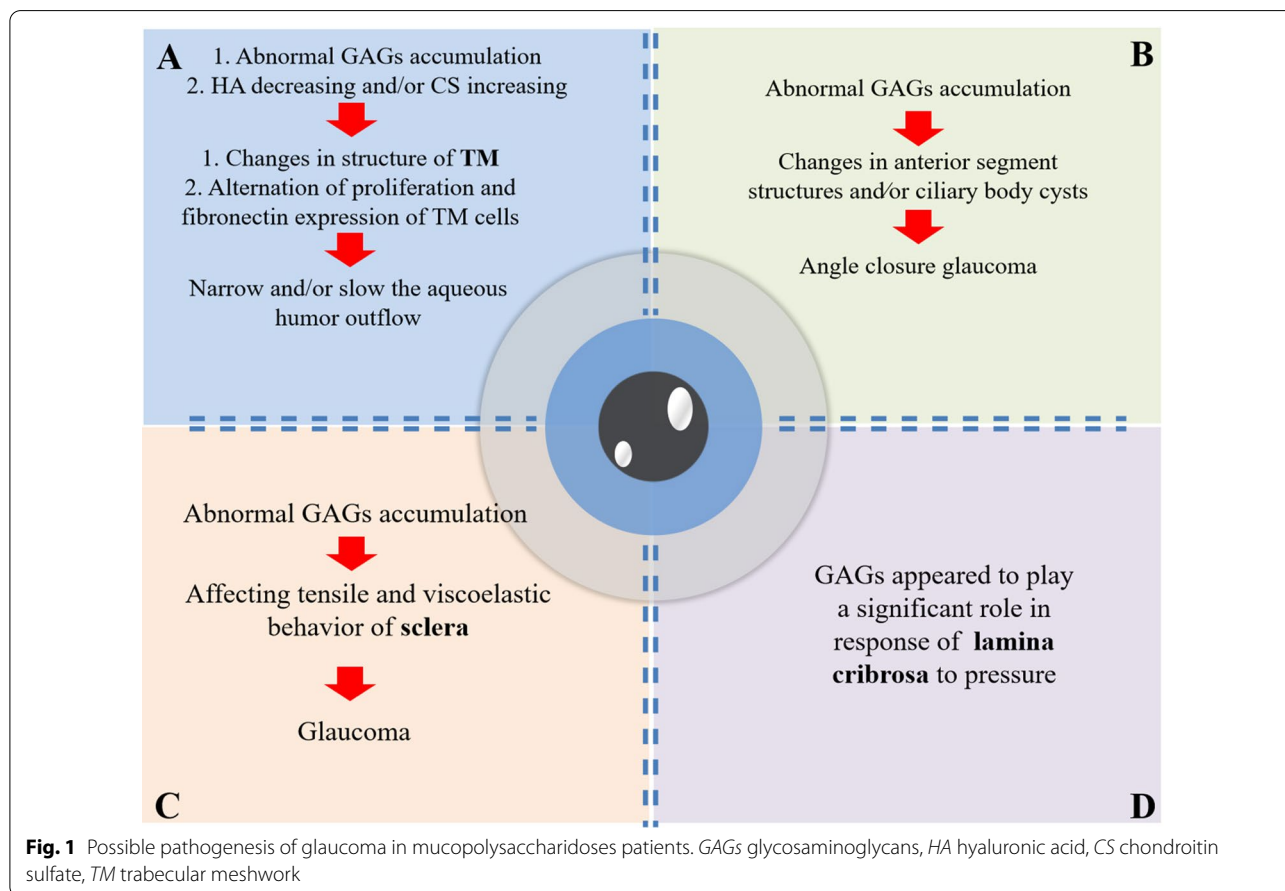
Glaucoma was known to be related with MPS I [12–17], MPS IV [18] and MPS VI [19–22], but it was rarely reported in the other subtypes of MPS. Until 2015, there was only one MPS II patient that was diagnosed with suspected glaucoma [23]. Ashworth et al. (2015) reported the first case series to assess and diagnose suspected glaucoma in patients with MPSs and to determine its prevalence [11]. In the report of Ashworth et al. (2015), there were 4 patients with MPS I, 2 patients with MPS II, 1 patient with MPS IVA, and 7 patients with MPS VI [11]. To the best of our knowledge, only one case with MPS III was reported to have glaucoma [24], while patients with MPS VII and IX were never reported to show glaucoma.

**Possible pathogenesis of glaucoma in MPSs**

Clinical manifestations of MPSs were caused by abnormal accumulation of GAGs, which were long and unbranched heteropolymers with repeating disaccharide units that were made up of carbohydrate moiety of

proteoglycans [25]. GAGs were widespread both in extracellular matrix and at cell surface. Biological functions of GAGs included regulation of cell growth and differentiation, tissue hydration maintenance and structure stabilization [26]. Distribution and function of GAGs in the development, homeostasis and pathology of ocular surface were discussed by Puri et al. (2020), clarifying how GAGs correlated with pathology [26]. Maric et al. (2019) revealed that newly diagnosed glaucoma patients had higher concentration of GAGs than those without glaucoma and implicated the relationship between GAGs and glaucoma [27].

The main risk factor for glaucoma is increased IOP, which may be caused by dysfunction of trabecular meshwork (TM) (Fig. 1A). TM locates within iridocorneal angle and is the main pathway for drainage of aqueous humor [28]. In 1954, Barany found that perfusion of aqueous outflow system with testicular hyaluronidase (degrading enzyme for GAGs) could increase facility of outflow [29]. The interesting phenomenon attracted lots of efforts to explore morphological features and biochemical values of GAGs in the pathway for drainage of aqueous humor.



**Fig. 1** Possible pathogenesis of glaucoma in mucopolysaccharidoses patients. GAGs glycosaminoglycans, HA hyaluronic acid, CS chondroitin sulfate, TM trabecular meshwork

Numerous GAGs and proteoglycans were expressed in TM [30]. At least six distinct classes of GAGs were recognized in TM: chondroitin sulfate (CS), dermatan sulfate (DS), heparan sulfate (HS), heparin sulfate (Hep), keratan sulfate (KS), and hyaluronic acid (HA, also known as hyaluronan) [31]. Five of them were related with MPSs [6]. Different kinds of GAGs performed different functions in TM. HA decrease and/or CS increase could narrow and/or slow the aqueous humor outflow [32]. The phenomenon was also observed in other reports about glaucomatous eyes of rabbits and humans [33, 34].

The relationship between GAGs and TM was not only studied at the animal level, but also explored at the cell level. Proliferation and fibronectin expression of TM cells were affected by pore size, alignment and composition of GAGs. This work provided insight into how the architecture and composition of collagen-GAGs scaffolds affected TM cells behavior [35].

Open angle glaucoma may be caused by abnormal GAGs deposition within TM, while angle closure glaucoma may result from abnormal accumulation of GAGs in anterior segment structures and/or ciliary body cysts [36, 37] (Fig. 1B). Glaucoma was firstly reported by Quigley et al. (1975) in two siblings with MPS I-S, who showed a sudden increase in IOP [16]. Quigley et al. (1975) speculated that the thickening of anterior ocular structures due to abnormal storage of acid mucopolysaccharide was the reason for angle closure glaucoma [16]. In patients with MPS VI, ultrasound images revealed that angle closure glaucoma was induced by shallow anterior chamber and thickened cornea with very thick retinal-choroidal-scleral [22].

Coudrillier et al. (2012) reported that thickness and biomechanical response differed between human glaucoma eyes and normal eyes [38]. Contribution of GAGs to tensile response of posterior sclera was confirmed in porcine and human eyes [39, 40]. GAGs may affect tensile and viscoelastic behavior of sclera and then causes glaucoma; however, more evidence in support of this speculation is needed (Fig. 1C).

Evaluation of optic nerve head (ONH), where retinal ganglion cell axons exit in the eye, is important for diagnosis and management of glaucoma [41]. Stress and strain state of ONH is strongly influenced by IOP and mechanical properties of lamina cribrosa [42]. Lamina cribrosa, the weakest part of sclera, bulges outward when IOP is raised chronically in the condition of glaucoma [43]. Contribution of GAGs to mechanical behavior of human lamina cribrosa was investigated by ex vivo inflation test. Results showed that GAGs were critical for the response of lamina cribrosa to pressure [44]. Tezel et al. (1999) observed increased levels of autoantibodies recognizing GAGs in lamina cribrosa of glaucomatous

eyes; however, the precise role played by autoantibodies for GAGs in ONH of glaucoma patients requires more research [45] (Fig. 1D).

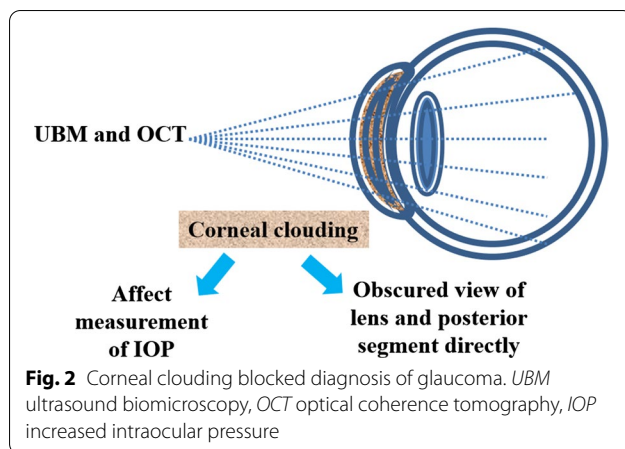
#### Diagnosis of glaucoma in MPSs

Patients with MPSs could develop glaucoma due to abnormal accumulation of GAGs, yet it was rarely reported in those patients. The following reasons could account for this phenomenon: (1) life span of patients with MPSs was usually not long enough to show obvious clinical manifestations of glaucoma; (2) non-ocular clinical manifestations of MPSs, including cognitive impairment and bone diseases, hindered diagnosis of glaucoma; (3) corneal clouding could block examination of inner contents of eyes and affect IOP measurement.

Age is an established risk factor for glaucoma [46]. Except for a few mild cases, MPSs is ultimately fatal with an average life expectancy of one to two decades if untreated [47]. MPSs patients could not live long enough to show obvious clinical manifestations of glaucoma, which may cause doctors to ignore this non-fatal manifestation. Limited language of young age patients with MPSs made it impossible for them to communicate changes in vision. More and more MPSs patients with glaucoma would be diagnosed, because the development of treatment would contribute to improvement of life span.

Non-ocular clinical manifestations of MPSs were also obstacles to diagnosis of glaucoma. Clinical manifestations of MPSs that blocked communication, including hearing loss and mental-retardation, may hinder doctors from understanding the condition of patients with MPSs [2, 48]. MPSs patients with bone diseases may have difficulty in posing for evaluation/imaging [49].

Corneal clouding, which was caused by abnormal accumulation of GAGs in corneal, did not block communication but could hinder diagnosis of glaucoma [50]. It was common in all subtypes of MPS but more frequent in MPS IH, MPS IH-S, MPS VI, and MPS VII [50]. Corneal clouding was found in approximately 70% of patients, with median age of 4 years old for MPS I H/S and 10 years old for MPS IS [51]. Lin et al. (2019) reported that all patients with MPS I and MPS VI and 94% of MPS IV patients had various degrees of corneal opacity in their retrospective research [52]. Corneal clouding did not only block the examination of the lens and posterior segment (vitreous and retina), but also affected IOP measurement by changing corneal thickness (Fig. 2). Wasielica-Poslednik et al. (2015 and 2017) confirmed positive correlation between corneal opacity and value of IOP. Meanwhile, they reported that IOP-values of eyes with strongly affected corneas (grade 4 in MPSs) were overestimated [53, 54]. Based on the conclusion,



IOP-values in reports of Lin et al. (2019) may be overestimated [52].

IOP should be tested by the same, individually adjusted and well-tolerated devices during follow-up of MPSs patients since different tonometry methods may result in variable IOP-values. Goldmann applanation tonometry, the gold standard for IOP measurement, was less dependent on corneal properties, making it more reliable for measuring IOP of patients with MPSs [55]. Ocular response analyzer and iCare rebound tonometer were tested and proved to be attractive alternatives to applanation tonometry in MPS patients [54]. Ultrasound biomicroscopy and optical coherence tomography played an increasingly important role in diagnosis of glaucoma in MPSs patients, because they could provide detailed views of anatomy behind cornea clouding (Fig. 2) [56].

A group of paediatric ophthalmologists, an orthoptist and an optometrist with extensive experience in children with MPSs, held a meeting in Stockholm in September 2010 and drew up clinical guidelines for diagnosis and management of ocular manifestations of MPSs [57]. The guidelines gave an overview of basic ocular assessments and a number of optional tests for children with MPSs. Diagnosis of glaucoma in MPSs patients could also follow European glaucoma society terminology and guidelines for glaucoma (4th Edition) [58, 59].

### Management of glaucoma of MPSs

Treatments for glaucoma in MPSs patients could follow the clinical guidelines for glaucoma: (1) initial therapy was topical medication or laser trabeculoplasty; (2) if patients failed to attain the target IOP during follow-up, additional therapies should be considered, such as trabeculectomy, non-penetrating deep sclerectomy and/or other glaucoma surgeries [60]. In addition to traditional treatments for glaucoma, hematopoietic stem cell transplantation (HSCT) for MPS-IH patients may show good

results for glaucoma treatment, though it needs more exploration [61]. Although enzyme replacement therapy (ERT) was safer than HSCT, effect of ERT on ocular manifestations was limited and variable [62]. Corneal clouding of MPS I and MPS VI patients could remain stable after ERT [63–65]. ERT also could maintain stability of sclera thickness of MPS I and MPS VI patients [66]. ERT was also tried to treat glaucoma in MPS VI patients; however, no changes were observed [67]. Retina–brain barrier and the avascular nature of cornea may reduce clinical efficacy of ERT for treating eye pathology. With the development of treatment, prevalence of glaucoma would be higher, because MPSs patients who were treated by approved therapies would get longer life span.

Current knowledge about the benefits and risks of anti-glaucoma therapies for MPSs patients is limited, because MPSs patients with glaucoma were rarely reported. A multicenter retrospective case note review reported the impact of medical treatments on IOP of 12 eyes from MPSs patients with glaucoma: IOP of 7 eyes was reduced; 1 eye was less successfully treated; 2 eyes stopped receiving treatment; IOP of 1 eye was reduced after keratoplasty [11]. The results were compliant with former reports: some reports showed improvements in IOP or vision after anti-glaucoma treatments [14, 15]; however, other reports showed that anti-glaucoma treatments were not good enough [17].

### Limitation

(1) Reports of glaucoma in MPSs patients were rare; reports about results of anti-glaucoma therapies for MPSs patients with glaucoma were rarer. Limited data hampered efforts to have a full view of prevalence of glaucoma in MPSs patients, benefits and risks of anti-glaucoma therapies, among other aspects. (2) Pathogenesis of glaucoma in MPSs patients was not clear, although a handful of reports explored the pathogenesis.

### Conclusion

Abnormal accumulation of GAGs may cause glaucoma in MPSs patients by affecting functions and structures of eye, including TM, cornea, ciliary body and sclera. Clinical manifestations and shortened life span could hamper diagnosis of glaucoma in MPSs patients and block knowledge accumulation on the benefits and risks of anti-glaucoma therapies. Despite the fact that cases of glaucoma in MPSs patients were rarely reported, prevalence of glaucoma in MPSs patients (ranged from 2.1% to 12.5%) indicated that glaucoma in MPSs patients was worthy of attention and further study so that quality of life for MPSs patients could be improved.

## Abbreviations

MPSs: Mucopolysaccharidoses; GAGs: Glycosaminoglycans; MPS: Mucopolysaccharidosis; IOP: Intraocular pressure; TM: Trabecular meshwork; CS: Chondroitin sulfate; DS: Dermatan sulfate; HS: Heparan sulfate; Hep: Heparin sulfate; KS: Keratan sulfate; HA: Hyaluronic acid; ONH: Optic nerve head; HSCT: Hematopoietic stem cell transplantation; ERT: Enzyme replacement therapy.

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## Authors' contributions

KWJ searched and collected related articles, then wrote the manuscript. ZJ collected related articles. KWJ and LC separately reviewed all related articles. DYX and MY supervised collection, screening of articles and data analysis, and they also revised writing of the article. All authors read and approved the final manuscript.

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## Availability of data and materials

Data can be made available from the corresponding author after discussion with the Institutional Review Board.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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