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Posterior segment findings in Hunter Syndrome: Case report and review

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ABSTRACT

Case Report and Case Series.

Purpose: To report a case of retinopathy in a 32-year-old man with Mucopolysaccharidosis type II (MPS II, Hunter syndrome) and highlight the unique multimodal imaging findings that can aid in diagnosing this rare condition.

Observations: We present a case of a 32-year-old Hispanic male who presented to the retina clinic following referral from optometry to evaluate for retinitis pigmentosa. He complained of difficulty driving at night and photophobia for 3 years. Visual acuity was 20/25 without correction in the right eye and 20/50 with pinhole correction in the left eye. Fundus examination was notable for bilateral fairly symmetric pigmentary changes along the retinal arcades. OCT revealed blunted foveal contour, perifoveal outer retinal thinning with central sparing in both eyes, and thickening of the external limiting membrane. Fundus autofluorescence showed a central parafoveal hyperautofluorescent ring and diffuse granular hypoautofluorescence in a symmetric bull's eye pattern.

Conclusions and Importance: The multimodal imaging findings from this case of a 32-year-old male with ocular manifestations of MPS II are characteristic of this rare condition. Recognizing these findings may aid in the diagnosis and subsequent management of patients with MPS II.

1. Introduction

Mucopolysaccharidoses (MPS) are lysosomal storage disorders caused by inherited defects in the glycosaminoglycan metabolic pathways.[1] There are nine MPS disorders that have been classified by enzyme defect and clinical features.

Unlike the other MPS disorders which are autosomal recessive, mucopolysaccharidosis type II (MPS II, Hunter Syndrome) is inherited in an X-linked pattern. As an X-linked disorder, MPS II most commonly affects males, although a few cases have been reported in females.[2] The incidence rate of MPS II has been reported as 0.38–1.09 per 100,000 live male births, making this condition exceedingly rare.[3] The incidence of MPS II in Hispanic individuals has not been reported. The incidence at a referral center in Mexico is estimated to be 0.15 per 100,000 total births, and all cases were observed in males.[4]

MPS II is caused by a deficiency of iduronate-2-sulfatase (IDS) on chromosome Xq28 resulting in defective glycosaminoglycan catabolism.[1] Without effective catabolism, patients with Hunter Syndrome accumulate glycosaminoglycans throughout the body.[1]

Classic features of all MPS types include characteristic thickening of facial features with an enlarged tongue, abnormalities in intellectual development, joint deformities, cardiopulmonary compromise, hearing loss, and ophthalmic complications. In patients with MPS of any type, glycosaminoglycan deposition has been found in most ocular tissue layers.[5] Visual impairment in MPS patients often results from corneal opacification, retinopathy, or raised intraocular pressure.[5]

MPS II presents with greater degrees of exophthalmos, hypertelorism, papilledema, and pigmentary retinopathy compared to other MPS types. Of note, the cornea is typically clear macroscopically in patients with MPS II, which is a contrasting feature to the severe corneal clouding appreciated in MPS type I.[6] In patients with MPS II, heparan sulfate glycosaminoglycans have been found prominently in the retinal pigment epithelium, ganglion cell layer, and retinal nerve fiber layer.[7] Furthermore, bilateral and symmetric optic nerve head crowding in patients with MPS II have also been described likely due to GAG deposition in the subarachnoid space leading to optic nerve compression.[8,9]

Histopathologic findings in MPS II have shown retinal changes resembling retinitis pigmentosa including the loss of peripheral

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photoreceptors and destruction of the retinal pigment epithelium (RPE) layer.[10] Patients presenting with retinal pigmentary abnormalities may complain of night blindness and decreased peripheral vision. The clinical findings may include arteriolar narrowing and retinal pigment epithelium narrowing.[5] Patients with MPS II may also present with bilateral epiretinal membranes and/or optic nerve compression due to disk swelling and thickening of the sclera.[5,11,12] Previously, ERG findings in Hunter syndrome patients have been described as reduced amplitude of a and b waves in the scotopic phase more than the photopic phase. ERG findings in 4 Hunter syndrome patients demonstrated progression at follow up visits, consistent with progressive rod-cone dystrophy.[13]

Management of the ocular manifestations of MPS II includes regular screening for vision impairment.[14] There is limited literature confirming the efficacy of *IDS* enzyme replacement therapy (ERT) in Hunter Syndrome, and its role in the management of the ocular manifestations of the disease is unclear.[15] The current ERT formulation approved for Hunter Syndrome does not cross the blood-brain barrier and may not cross the blood-retina barrier, limiting the efficacy in targeting retinal impairments or central nervous system manifestations.[16,17] Visual acuity and visual field improvement in a patient with Hunter Syndrome following ERT has been documented in a single case report in 2019.[16]

2. Case report

A 32-year-old male presented to the retina clinic for an evaluation for retinitis pigmentosa after being referred by optometry. The patient noted that he had hearing loss and poor vision throughout his life, which worsened about 10 years ago. He stopped driving at night due to issues with glare and complained of photophobia for the last 2–3 years.

His visual acuity without correction was 20/25 in the right eye and 20/50 with pinhole correction in his left. His refractive error was minimal, measuring +0.75 in his right eye and +0.50 in his left eye. He was noted to have amblyopia in his left eye, likely from longstanding exotropia. His intraocular pressures and pupils were normal. His external exam was notable for exotropia, short stature, coarse facial features, prominent supraorbital ridges, thick lips, hypertelorism, bilateral frontal and temporal bossing, and macrocephaly. His anterior segment exam was grossly unremarkable. The patient's optic nerves demonstrated good color with sharp margins and a normal cup to disc in both eyes, without evidence of pallor in both eyes. Retinal vessels appeared normal. The fundus exam was notable for bilateral fairly symmetric pigmentary changes along the retinal arcades in a bull's eye pattern, most notable on autofluorescence. Our patient did not undergo electroretinogram (ERG) testing.

All imaging studies have been displayed in Fig. 1 Optical coherence tomography (OCT) demonstrated perifoveal loss of outer segments with preservation of ellipsoid and thickened external limiting membrane at the fovea. Abnormal scleral contour with a blunted foveal contour, and parafoveal outer retinal thinning with central sparing in both eyes was appreciated on OCT (see Fig. 1). Fundus autofluorescence showed a hyperautofluorescent parafoveal ring and diffuse granular hypoautofluorescence in a symmetric bull's eye pattern that corresponded to the areas of pigmentary changes along the vascular arcades on wide-field fundus photography (see Fig. 2 and 3).

Upon further chart review, it was discovered that he was previously diagnosed with Mucopolysaccharidosis type II (Hunter Syndrome) 15 years prior. Genetic testing results indicate a missense variant of NM_000202.8(*IDS*):c.1265G > T. This is a known pathogenic variant.[18] The patient's variant was identified by Sanger sequencing of the *IDS* gene at Greenwood Genetics, a CLIA certified laboratory. His most recent urinary glycosaminoglycan level was 9.17 [normal 0–6.5 mg/mmol creatinine] and heparan sulfate level was 12.60 [normal 0–1.07 g/mol creatinine] on 6/23/2021. There is no documentation of the specific genetic variant or consanguinity in the patient's family. His family history is significant for a brother with Hunter Syndrome who passed away. The patient has been compliant on enzyme replacement therapy with intravenous Idursulfase weekly since April 2009. It was elected to see him annually to assess for any progression and/or changes.

3. Discussion

In this case report, we describe the retinal findings of a 32-year-old male with MPS II who was initially referred for concerns of retinitis pigmentosa. In addition to ophthalmic complications, the patient presented with typical systemic features of MPS II including short stature, coarse facial features, and hearing loss. There are limited reports in the literature on the presentation and pathogenesis of specific retinal changes in patients with MPS II. The use of multimodal imaging techniques, however, allows for more detailed description of retinal findings in patients with Hunter syndrome and may help understanding of this rare entity.

Our patient's fundus examination was notable for bilateral symmetric RP-like pigmentary changes along the arcades with perifoveal outer retinal thinning that spared the parafoveal area. Fundus autofluorescence revealed a characteristic prominent bilateral symmetric ring of hyperautofluorescence that correlated with ellipsoid attenuation and intact ELM with an adjacent ring of hypoautofluorescence that correlated with outer segment loss. Notably, ELM was thickened which has been previously described.[7,8] It is posited that a thickened external limiting membrane of the central fovea may result from GAG degradation products in retinal Müller cells.[19] The distinct bull's eye pattern has been previously described in cases of mucopolysaccharidoses, although the pathogenesis of this phenotype has not been proven.[9,19] Thus,

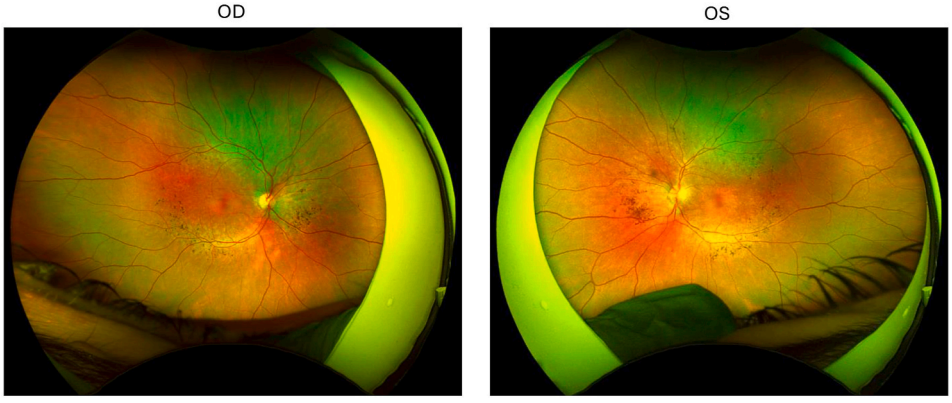

Fig. 1. *Optical Coherence Tomography (OCT) Images in Hunter Syndrome.* OCT images of both eyes in a 32-year-old male with Hunter Syndrome demonstrating blunting of the foveal contour with perifoveal outer nuclear and ellipsoid attenuation with a thickened external limiting membrane.

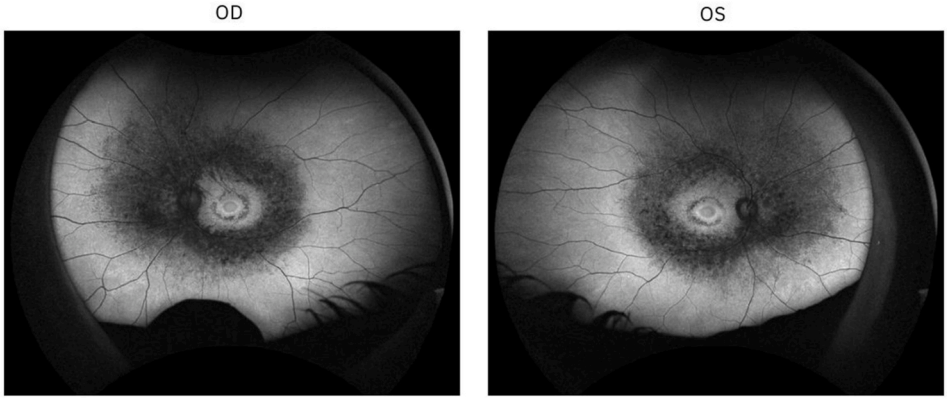

Fig. 2. *Wide Field Fundus Photographs in Hunter Syndrome.* Wide-field fundus photographs of both eyes in a 32-year-old male with Hunter Syndrome demonstrating the symmetric bilateral pigmentary changes along the vascular arcades OU.

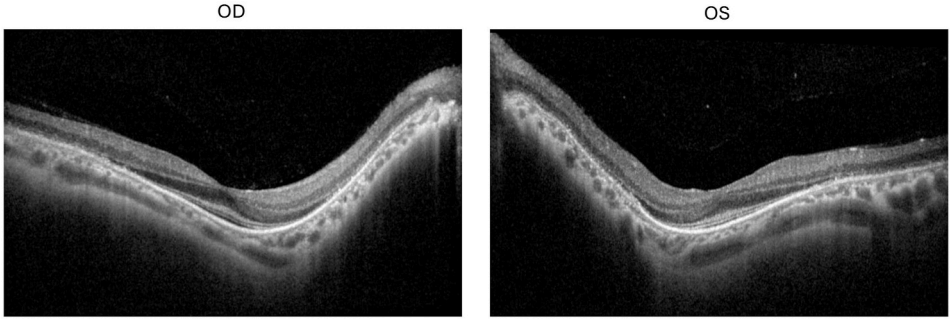

Fig. 3. *Fundus Autofluorescence Images in Hunter Syndrome.* Fundus autofluorescence images of both eyes in a 32-year-old male with Hunter Syndrome demonstrating parafoveal hyperautofluorescent rings correlating with ellipsoid attenuation and intact ELM with adjacent rings of hypoautofluorescence as well as diffuse, granular hypoautofluorescence along the arcades correlating with outer segment loss and pigmentary changes.

despite the RP-like pigmentary changes along the arcades, the presence of thickened ELM and absence of bony spicules on fundus examination differentiate the presentation of MPS II from typical retinitis pigmentosa. Previous studies indicate that the observed perifoveal outer retinal thinning in mucopolysaccharidoses may result from loss of photoreceptors and diffuse loss of the retinal pigment epithelium.[8,20] This mechanism is thought to be related to proteoglycan accumulation in the retinal interphotoreceptor matrix (IPM), which is largely involved in the maintenance of photoreceptor viability. Lazarus et al. examined the IPMs of MPS VII mice by various histochemistry modalities and found that CS proteoglycan accumulation in the IPM due to errors of GAG catabolism dismantles the IPMs photoreceptor-supportive structure and leads to subsequent photoreceptor degeneration.[21] Although the accumulated proteoglycan in MPS II is heparan sulfate rather than CS, the mechanism of photoreceptor loss in MPS II may be similar to MPS VII as immunopositive reactions for CS, heparan sulfate, dermatan sulfate, and hyaluronan have all been found in the IPM of human eyes.[22]

Previous studies have used additional diagnostic modalities to describe findings that may aid in the diagnosis of MPS II. A 2007 case report of a 42-year-old male with MPS II employed multifocal electroretinography and OCT to reveal bilateral reduction in foveal responses, a notably normal retinal nerve fiber layer, and thinning of the outer retinas. Additionally, small foveal and parafoveal cystoid spaces were described in the inner retina bilaterally.[8]

Management for patients with ocular manifestations of MPS II should include regular vision screening. Our patient presented to us on enzyme replacement therapy with diffuse outer segment loss outside of the parafoveal region. Although visual acuity and visual field improvement in Hunter Syndrome following ERT has been reported, the role of enzyme replacement therapy in the management of MPS II retinopathy has not been well described.[1]

4. Conclusions

Multimodal imaging findings of MPS II may contribute to early diagnosis and systemic treatment of this rare condition. Diffuse pigmentary changes similar to retinitis pigmentosa without bony spicules and notably thickened central ELM with a parafoveal ring of hyperautofluorescence should warrant consideration of a lysosomal storage disorder, especially in a patient fitting the clinical phenotype.

Institutional Review Board approval

Institutional Review Board approval was not obtained for this report.

CRediT authorship contribution statement

Ishani P. Majmudar: Writing – review & editing, Writing – original draft. **Haroon O. Ismail:** Writing – review & editing, Writing – original draft. **Suveera Dang:** Writing – review & editing, Writing – original draft. **Manjot K. Gill:** Writing – review & editing, Supervision.

Patient consent

Formal consent to publish the case report was obtained from the patient.

Authorship

All authors attest that they meet the current ICMJE criteria for

Authorship.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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