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Case Report

Retinal Changes in Patients with Type 1 and Type 2 Mucopolysaccharidosis

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ABSTRACT

Purpose: Mucopolysaccharidosis (MPS) are a group of lysosomal storage disorders caused by inborn Glycosaminoglycans (GAG) metabolism errors. In both MPS type I and II there is an accumulation of heparan sulfate and dermatan sulfate. This work aims to describe retinal findings in patients with MPS I and MPS II. A cross-sectional case study including 2 patients with MPS I (patients 1 and 2) and 1 patient with MPS II (patient 3) was performed. A multimodal imaging was performed using color fundus photography, Spectral Domain Optical Coherence Tomography (SD-OCT) and Near-Infrared Reflectance (NIR) imaging.

Case presentation: Patient 1, with Hurler syndrome presented in the SD-OCT, an increased thickness of the hyper reflective band of the External Limiting Membrane (ELM) in the foveal area. In the parafoveal and perifoveal regions, SD-OCT displayed loss of the interdigitation, ellipsoid and myoid zones, loss of the ELM and thinning of the Outer Nuclear Layer (ONL). Patient 2, with Hurler-Sheie syndrome, presented in the SD-OCT, an increased thickness of the hyper reflective band of the ELM in the foveal area. Patient 3, with Hunter syndrome, presented bilateral pigmentary atrophic changes at the mid-peripheral retina. SD-OCT assessment revealed thickening of the hyper reflective band of the ELM in the foveal area. Beyond the parafoveal area, the ellipsoid zone band, EML and ONL were absent.

Conclusion: MPS I and II, despite involving different enzyme deficiencies and having different inheritance patterns, accumulate the same type of GAGs and present a similar pattern of retinal changes, particularly involving the outer retina.

Key words: Mucopolysaccharidosis; Hurler syndrome; Hurler-scheie syndrome; Hunter syndrome; Retina; Macula

INTRODUCTION

Mucopolysaccharidoses (MPS) are a heterogeneous group of lysosomal storage disorders caused by intra and extracellular accumulation of Glycosaminoglycans (GAGs). The accumulation results from a deficiency of different enzymes along these polysaccharide breakdown pathways. Depending on the affected enzyme there are seven groups of MPS, with different subtypes [1,2].

MPS type I is defined by a deficiency of lysosomal hydrolase α-l-iduronidase, which is required to break down heparan and dermatan sulfate. The phenotypic spectrum of α-l-iduronidase deficiencies includes the mildest form (Scheie syndrome), the intermediate form (Hurler-scheie syndrome) and the severe form (Hurler syndrome). The affected gene is *Alpha- L -Iduronidase (IDUA)*.

MPS type II is defined by a deficiency of iduronate-2-sulfatase, which results in the accumulation of dermatan and heparan sulfate. The affected gene is *Iduronate 2-Sulfatase (IDS)* at locus Xq28. It is the only MPS type inherited in an X-linked recessive inheritance pattern. MPS types I and II have different hereditary patterns and are caused by different enzyme deficiencies but result in the accumulation of the same metabolic products.

MPS-associated pigmentary retinopathy is usually a late manifestation and is known to occur to a variable degree in MPS I and MPS II. This work aims to present and compare retinal changes in two cases of MPS type I and one case of MPS type II. The patients had their diagnosis confirmed by genetic and biochemical analysis [3].

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CASE PRESENTATION

Case 1

A 15-year-old Caucasian female child with the diagnosis of MPS I (Hurler's syndrome) has a severe genotype (homozygous status for the mutation c.1293G>A; p.W402X, exon 9), associated to an alpha-iduronidase leucocyte level of 0 nmol/h/mg protein (normal range 11-93 nmol/h/mg) and urinary GAGs of 193 mg/mmol creatinine (normal range 6-16 mg/mmol creatinine) [4].

Currently, patient maintains peculiar phenotype with short stature, pectus carinatum, interstitial respiratory disease and mild cognitive impairment.

The patient began Enzyme Replacement Therapy (ERT) at 5 months of age and was submitted to Hematopoietic Stem Cell Transplantation (HSCT) at 12 months. The patient developed a severe graft *versus* host disease one month later. The patient was maintained on ERT for three years.

The Best Corrected Visual Acuity (BCVA) was 6/10 Oculus Uterque (OU). Slit lamp biomicroscopy showed intrastromal corneal deposits, more pronounced in the left eye. Intraocular pressure was 20 mmHg Oculus Dexter (OD) and 18 mmHg Oculus Sinister (OS) under dorzolamide 2% plus timolol 0.5% 2 id (Figures 1a and 1b).

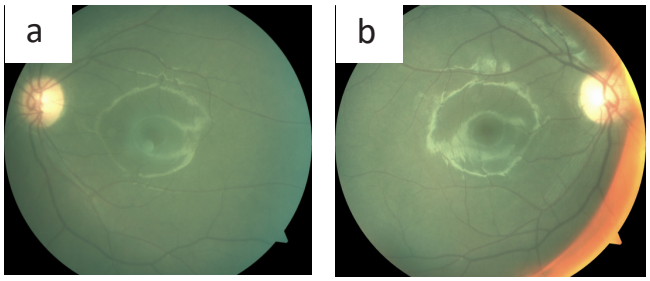

Figure 1: (a): Retinography of the right eye; (b): Retinography of the left eye.

Fundus examination was clinically normal and no pigmentary changes were observed. Nevertheless, patient SD-OCT assessment revealed increased thickness of the hyper reflective band of the External Limiting Membrane (ELM) in the foveal area in both eyes (Figures 2a and 2b).

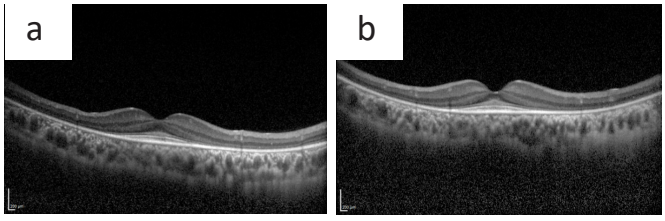

Figure 2: (a): Spectral Domain Optical Coherence Tomography (SD-OCT) horizontal scan of the fovea in the right eye; (b): Spectral Domain Optical Coherence Tomography (SD-OCT) horizontal scan of the fovea in the left eye.

The rest of the outer retina, namely the myoid, ellipsoid and interdigitation zones and the Retinal Pigment Epithelium (RPE)/Bruch's membrane complex presented no changes. In the parafoveal and perifoveal regions, SD-OCT displayed a loss of the interdigitation, ellipsoid and myoid zones, loss of the ELM and thinning and eventual loss of the ONL. Small cysts in the ONL, Inner Nuclear Layer (INL) and Ganglion Cell Layer (GCL) were also observed close to the fovea (Figure 3).

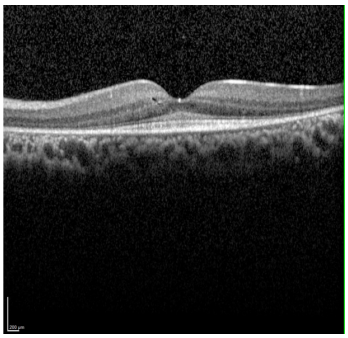

Figure 3: Spectral Domain Optical Coherence Tomography (SD-OCT) horizontal scan showing small cysts in the Outer Nuclear Layer (ONL) and Inner Nuclear Layer (INL).

The SD-OCT presentation is similar between 2019 and 2023. Fundus NIR imaging revealed a bilateral hyper reflective ring centered on the fovea that was more evident in the left eye (Figures 4a and 4b).

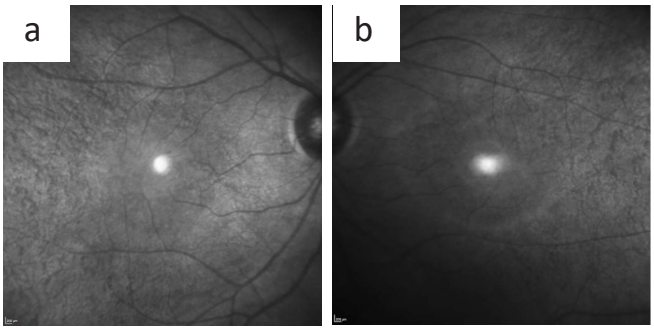

Figure 4: (a): Fundus Near-Infrared Reflectance (NIR) imaging of the right eye; (b): Fundus Near-Infrared Reflectance (NIR) imaging of the left eye.

Case 2

A 7-year-old girl with Hurler-Sheie syndrome had an apparent homozygous status for the mutation c.1598C>G, p.P533R. The enzymatic activity determination revealed an alpha-iduronidase leucocyte level of 0.1 nmol/h/mg protein (normal range: 11-93 nmol/h/mg protein) with 88 mg/mmol/creatinine urinary GAGs (normal range: 6-16 mg/mmol/creatinine). The patient had typical systemic features such as mild joint changes, joint stiffness, carpal tunnel syndrome, dental changes, mild aortic insufficiency, associated with skeletal dysostosis (lower ribs sketching image in rowing, flattening of the femoral heads and acetabulum) and slight cognitive impairment. The patient had already undergone tonsillectomy and myringotomy for recurrent otitis and snoring, surgery to correct the trigger thumb and surgery to repair a large umbilical hernia. The patient began Enzyme Replacement Therapy (ERT) at 5 years of age.

In the ophthalmology examination, patient presented a BCVA of 6/10 OU. Slit lamp biomicroscopy showed intrastromal corneal deposits, more pronounced in the left eye. Intraocular pressure was 19 mmHg OD and 21 mmHg OS, without medication.

The patient fundus examination appeared to be normal, with no pigmentary changes, but the SD-OCT assessment revealed in the foveal area in both eyes, an increased thickness of the hyper reflective band of the ELM. On the other hand, in the parafoveal and perifoveal regions, neither thinning nor loss of the outer layers was observed. No retinal cysts were identified. The patient fundus NIR imaging was normal. The patient sub foveal choroid was also remarkably thick and sub foveal choroidal thickness is OD 437 µm, OS 413 µm (Figures 5-7).

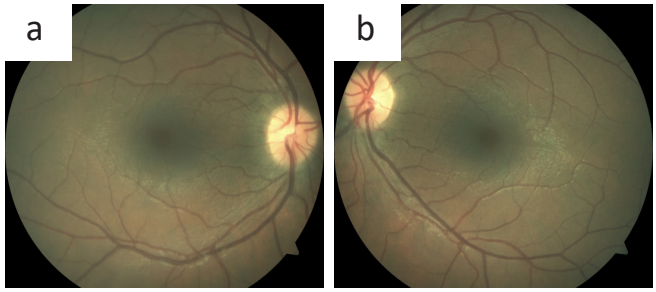

Figure 5: (a): Retinography of the right eye; (b): Retinography of the left eye.

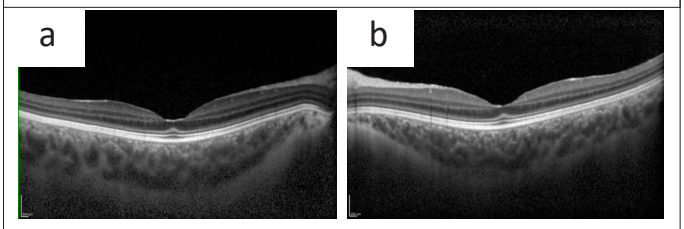

Figure 6: (a): Spectral Domain Optical Coherence Tomography (SD-OCT) horizontal scan of the fovea in the right eye; (b): Spectral Domain Optical Coherence Tomography (SD-OCT) horizontal scan of the fovea in the left eye.

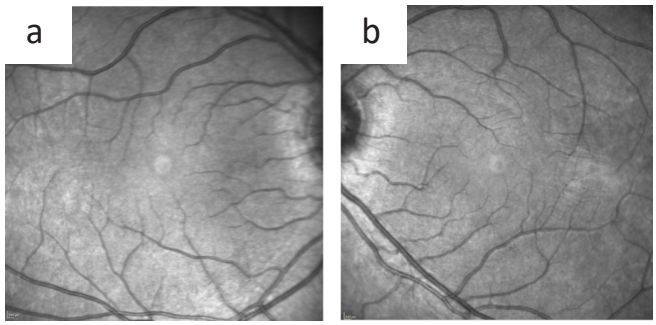

Figure 7: (a): Fundus Near-Infrared Reflectance (NIR) imaging of the right eye; (b): Fundus Near-Infrared Reflectance (NIR) imaging of the left eye.

Case 3

A 25-year-old man, with Hunter syndrome, had a hemizygous status for the mutation c.1122C>T in exon 8 of *IDS* gene. The patient analysis revealed an Iduronate-2-sulphatase enzyme activity of 0.00 µmol/l/h. Systemic involvement including macrocephaly, upper airway obstruction, mild pulmonary restriction, cardiomyopathy, hepatosplenomegaly, umbilical hernia, skeletal dysostosis, mild joint stiffness, severe hypoacusia and slight cognitive impairment [5].

The patient had been diagnosed at the age of 15 months and started enzyme replacement therapy with idursulfase in 2006, when it started being available in our country. The patient presented a BCVA of 9/10 OU. Slit lamp biomicroscopy was unremarkable. Intraocular pressure was 12 mmHg OU, without medication.

Fundus examination revealed bilateral pigmentary atrophic changes at the mid-periphery of the retina that spared the central macula (Figures 8a and 8b).

SD-OCT assessment revealed a thickening of the hyper reflective band of the ELM in the foveal area (Figures 9a and 9b).

The ellipsoid zone band could not be tracked beyond the central 2 mm diameter ring, the ELM beyond the 2.5 mm diameter ring and the outer nuclear layer beyond the central 3 mm diameter ring. The internal retina was unremarkable. Fundus infrared imaging revealed a bilateral hyper reflective ring centered on the fovea (Figures 10a and 10b).

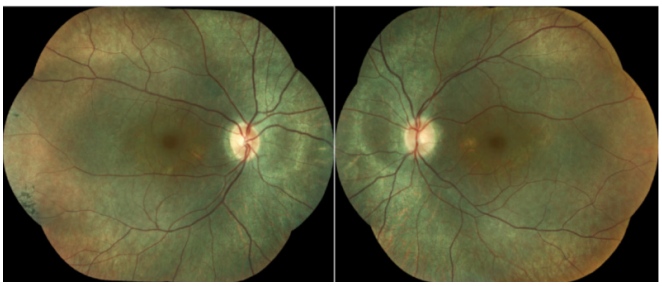

Figure 8: (a): Fundus retinography of the right eye; (b): Fundus retinography of the left eye.

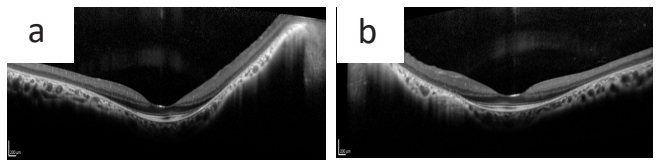

Figure 9: (a): Spectral Domain Optical Coherence Tomography (SD-OCT) horizontal scan of the fovea in the right eye; (b): Spectral Domain Optical Coherence Tomography (SD-OCT) horizontal scan of the fovea in the left eye.

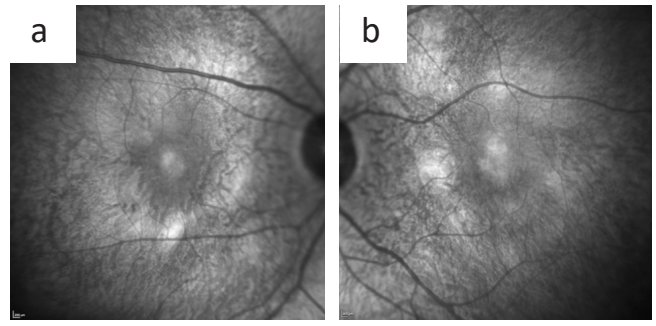

Figure 10: (a): Fundus Near-Infrared Reflectance (NIR) imaging of the right eye; (b): Fundus Near-Infrared Reflectance (NIR) imaging of the left eye.

RESULTS AND DISCUSSION

The increase in the average life expectancy of patients with MPS and the more recent developments in ophthalmology imaging technology have promoted a better understanding and characterization of the ocular involvement of this group of diseases.

In the past, without the use of OCT, retinal changes were suspected by observation with indirect and direct ophthalmoscopy and angiography, as well as by registering a narrowing constriction of their visual fields [6].

Recently, Sornalingam K, et al., [7] commented on the importance of OCT in the detection of retinopathy and cystoid macular edema in MPS. They observed a hyper-reflective zone above the inner segment ellipsoid line in the central fovea in 16/20 eyes of patients with MPS type I.

Mack, et al., [8] described two cases with Scheie syndrome. A twenty-one-year-old male presented parafoveal thinning of retinal layers and sub foveal increased hyper reflectance at the level of the external limiting membrane with outer retinal layers intact. The patient had received IDUA for 8.75 years. The second case was a fifty-nine-year-old Caucasian female who presented parafoveal thinning of all layers, particularly the ellipsoid line and other photoreceptor components, with sub foveal increased hyper reflectance at the level of the ELM and peripheral macular photoreceptor lines fragmented. The patient was diagnosed with MPS I at age fifty-four years and received IDUA for 5 years with excellent compliance.

Kim, et al., [9] reported a case of a 5-year-old boy with Hunter syndrome who showed thickening of the ELM with no other abnormalities. These findings are similar to our case 2 a 6-year-old girl. Perhaps it can be suggested that retinal changes occur in phases over time, this being the first one.

Retinal cysts have been reported in MPS I and II 6-9. Huang, et al., [10] comment on a patient who had reversible cystic changes.

The similarity of retinal findings between MPS type 1 and 2 has already been highlighted by Huang, et al., [10] describing the presence of a thickened ELM, widening of the distance between the Retinal Pigment Epithelium (RPE) and ellipsoid zone at the fovea and disruption of the ellipsoid zone at the extrafoveal area in the OCT examinations. In 2015, Seok, et al., [11] found thinning of the parafoveal photoreceptor IS/OS in two MPS I patients and one MPS II patient and of the perifoveal photoreceptor Inner Segment (IS)/Outer Segment (OS) in two MPS I and in five MPS II patients. Curiously, all MPS I and II patients exhibited thickening of the central foveal ELM. All patients had undergone ERT.

In these two types of MPS, despite involving different enzyme deficiencies and having different inheritance patterns, the retinal chances are similar, which can be explained by the fact that the accumulated GAGs are the same, specifically dermatan sulfate and heparan sulfate. These alterations are more pronounced in the foveal zone, probably because the density of photoreceptors is greater, leading to a greater amount of GAG which overloads enzyme availability [12,13].

In recent years, the introduction of Hematopoietic Stem Cell Transplantation (HSCT) and ERT has greatly increased the lifespans of these patients and it has been speculated whether the early introduction of therapy can prevent the onset of ocular changes. Nonetheless, when ocular outcomes of post-treatment are mentioned, corneal opacity is often the only measure discussed, as has been shown by Aldenhoven, et al., [14].

About ERT, no beneficial effects have been identified on the ocular manifestations of MPS and it has been thought to be related to the blood-retina barrier and the avascular nature of the cornea. It has been thought that ERT does not cross the blood-brain barrier and presumably does not cross the blood-retina barrier either [15,16].

CONCLUSION

With this work, we expanded the knowledge of MPS-related retinal disorders. MPS I and II, despite involving different enzyme deficiencies and having different inheritance patterns, accumulate the same type of GAGs and present a similar pattern of retinal changes, particularly involving the outer retina. The increase in survival of these patients and recent developments in ophthalmology imaging technology have boosted our understanding of the different patterns of retinal involvement in the different types of disease. However, a 2009 study reported improved brain imaging abnormalities with ERT. Interestingly, in case 1, with two SD-OCT 4 years apart, the retinal changes seem superimposable. Further studies are needed to evaluate the relationship between macular changes and treatment.

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