Bull's eye maculopathy and subfoveal deposition in two mucopolysaccharidosis type I patients on long-term enzyme replacement therapy

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Abstract

Purpose: To report retinal findings in two patients with mucopolysaccharidosis type I (MPS I) receiving human recombinant alpha-L-iduronidase (Laronidase) as enzyme replacement therapy.
Observations: Patient 1 had visual acuity 20/20 right eye, 20/25 left eye and unremarkable anterior segment and retinal examination. Optical coherence tomography (OCT) scanning demonstrated parafoveal thinning and subfoveal hyperreflective material. Patient 2 had visual acuity 20/20 both eyes, with dense nuclear cataract both eyes. Retinal examination demonstrated bull’s eye maculopathy both eyes. OCT scanning confirmed parafoveal atrophy and demonstrated similar appearing subfoveal hyperreflectant material, more prominent than in case 1.

Conclusions and importance: These two patients with MPS I receiving Laronidase treatment have developed bull’s eye maculopathy changes and subfoveal deposition of hyperreflectant material despite excellent compliance and good tolerance of the standard dose of enzyme therapy for this disorder. Further studies are required to determine the nature of the material, the incidence and the effect of enzyme replacement therapy on these findings in patients with MPS I.

1. Introduction

Mucopolysaccharidosis type I (MPS I, OMIM #607016) is an autosomal recessive lysosomal storage disorder due to deficiency of alpha-L-iduronidase (IDUA), of prevalence approximately 1 per 88,000 live births in Australia. Gradual lysosomal accumulation of metabolites of IDUA glycosaminoglycan (GAG) substrates heparan and dermatan sulfate eventually interferes with cellular function. Although this process occurs in all cells, it is pathophysiologically most apparent in terminally differentiated, long-lived cells such as neurons, cardiomyocytes, and retinal pigment epithelium, underpinning the multisystem and progressive nature of the disorder.

Interference with normal bone development is clinically apparent in the dysostosis multiplex and typical facial dysmorphism that is characteristically developed in this disorder. Cardiorespiratory disease in the context of skeletal deformities and bronchial, pulmonary and cardiac pathology imparts significant morbidity and mortality. Terminable neurodegeneration, retinal degeneration, corneal clouding and cataracts contribute importantly to lifelong morbidity.

Phenotypic variability is wide, varying from severely affected individuals (Hurler syndrome, MPS I-H) to attenuated forms (Scheie syndrome, MPS I-S). Significant restrictive pulmonary disease and progressive neurodegeneration heralded in early childhood characteristically complicates the severe, Hurler phenotype, as opposed to the normal neurological development and sparing of cognition in the attenuated, Scheie phenotype.

Heterologous hematopoietic stem cell transplant (HSCT) has become the gold standard treatment for patients with the severe phenotype diagnosed under 2.5 years of age. Enzyme replacement

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therapy (ERT) with human recombinant IDUA (Laronidase, Genzyme, Cambridge MA) has demonstrated efficacy in mitigating a number of the clinical effects of the enzyme deficiency, most notably the effects on cardiopulmonary function, and is used for patients diagnosed later in life, as well as pre- and peri-HSCT.3,4

Reported ocular features of MPS I include corneal clouding, pigmentary retinopathy, optic nerve abnormalities including glaucoma, papilledema and atrophy, ocular motility and refractive problems.5 There is one report of macular edema-like change observed on stereoscopic fundus photography.6 Between 44% and 79% of MPS I patients have visual acuity less than 20/40 in their better eye.7 Retinal involvement, when present, has been described as a progressive rod-cone retinal degeneration with attenuated electroretinographic (ERG) amplitude with relatively mild clinically apparent retinal pigment epithelial (RPE) change in the mid periphery8,9 and typical degeneration of the outer retinal layers on histopathological examination. Patients without clinical retinal degeneration have been shown to have fine fibrillary inclusions in the RPE and retinal ganglion cells, and multimembranous inclusions in retinal ganglion cells.10 We are not aware of any published reports of macular histopathology in untreated patients with MPS I. Optical coherence tomography (OCT) studies have demonstrated thinning of the parafoveal ellipsoid line, thickening of the central foveal external limiting membrane (ELM), parafoveal retinal folds, retinal cysts and fluid in the outer nuclear layer in MPS I patients,11,12 some of whom received ERT.13 A recent report

Fig. 1. A twenty-one year old male with mucopolysaccharidosis type I undergoing Laronidase enzyme replacement therapy. A Color fundus photographs of the right and B left eye, showing slight foveal reddening, but no bull’s eye macular appearance. Images are blurred by corneal clouding. C Optical coherence tomography (OCT) scanning (Cirrus, Zeiss, Germany) of the right, and D left eye showing subfoveal hyperreflectant material at the level of the external limiting membrane. The key OCT features of photoreceptor structure appear intact. Inset OCT cube views demonstrate in both eyes parafocal thinning. E Multifocal ERG responses (Roland, Brandenburg, Germany) showing reproducible response only in ring 1 in the right eye (red arrow), and F no reproducible responses in the left eye. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
demonstrated improved vision in 42% of patients receiving Laronidase treatment; the study recorded visual acuity and corneal clouding, but not retinal structure or function. There are no reports of improved retinal function in patients receiving Laronidase treatment. ERT does not cross the blood-brain barrier and presumably does not cross the blood-retina barrier either, given the ultrastructural similarity between the two. We report macular changes in two patients with MPS I receiving ERT. Case 2 is the oldest reported patient, and the first report of a patient undergoing cataract surgery. We also report the first multifocal ERG analysis of MPS I patients. An earlier version of this work was published as a meeting abstract.

2. Findings

2.1. Case 1

A twenty-one year old Caucasian male was referred for baseline ophthalmological monitoring during ERT. He complained of glare. He had been diagnosed with MPS I 15 years prior, at the age of 6 when his mother sought clarification for his impaired mobility. He had the typical although relatively mild facial dysmorphic features, severe obstructive pulmonary disease, mild mitral valve stenosis and trace mitral regurgitation, hepatosplenomegaly and bilateral carpal tunnel syndrome. He had received IDUA at the regular dose of 0.58 mg/kg for 8.75 years with excellent compliance and tolerance. On examination, best corrected visual acuity was right 20/20 and left 20/25. Corneal haze bilaterally and were thin right 31.2 nV/deg²; lower limit of normal 42.5) Multifocal ERG findings Reproducible P1 responses only in ring 1 in the right eye (31.7 nV/deg²; lower limit of normal 42.5).

2.2. Case 2

A fifty-nine year old Caucasian female was referred for ophthalmological monitoring during ERT. She complained of nyctalopia onset aged 31 years. She was diagnosed with MPS I in 2011 at age fifty-four years, and has involvement of bones and joints, with relatively mild facial dysmorphism which had been interpreted as acromegalic in years previous to the diagnosis of MPS I, obstructive pulmonary disease, aortic valve disease and bilateral carpal tunnel syndrome. In keeping with the Australian Life Saving Drugs Program guidelines, she has received IDUA at a dose of 0.58 mg/kg ideal body weight (adjusted for BMI 27) for 5 years with excellent compliance and tolerance. On examination, best visual acuity was 20/20 in both eyes. Corneal haze was right 1.5 mm, left 1.46 mm. Many posterior synchiae were present, and minimal pupil dilation could be induced pharmacologically. On fundoscopy optic discs demonstrated cup to disc ratios of 0.3 and appeared healthy, a bull’s eye maculopathy pattern was noted along with sparse patches of intraretinal pigment migration (Fig. 2). She readily dissociated to a large alternating exotropia. OCT scanning demonstrated parafocal thinning of all layers, particularly the ellipsoid line and other photoreceptor components, with subfoveal increased hyperreflectance at the level of the ELM, and peripheral macular photoreceptor lines fragmented. Full-field ERG (Table 1) showed no reproducible pure rod responses, with attenuated responses, negative in waveform in the right eye, to brighter dark-adapted stimuli. Photopic responses were reduced in amplitude and prolonged in latency. Multifocal ERG showed reproducible responses only in ring 1 in both eyes.

She was monitored annually for three years. Nuclear sclerosis developed in both eyes, and anterior chambers progressively shallowed. She underwent uneventful bilateral YAG laser peripheral iridotomy. Her clinical examination and electrophysiology testing was otherwise stable. She developed blurred vision and visual acuity fell to right 20/32 and left 20/40 due to cataract. She underwent laser-assisted cataract surgery in both eyes, with implantation of Rayner C-Flex 970C posterior chamber lenses right.
eye +39D and left eye +38D. Post-operatively best visual acuity was right 20/32 and left 20/25, however cystoid macular edema (CME) developed at post-operative week 8 (Fig. 2), treated with topical prednisolone acetate 1% and ketorolac 0.5%, with slow improvement in visual acuity and OCT signs. At last review, visual acuity was right 20/32, left 20/25 and topical treatment was slowly withdrawn.

3. Discussion

In this study, we report parafoveal thinning, particularly at the level of the ellipsoid line, and thickening of the foveal ELM, similar to previous reports. Case 2 is one of the oldest patients reported to date, and the first reported patient to undergo cataract surgery. We also include the first multifocal ERG investigation of macular dysfunction. The older of the two patients (59 years) reported on here has more marked findings with a frank bull's eye maculopathy and mild CME, which worsened immediately following cataract surgery. Additionally, results consistent with a typical rod-cone dystrophy were evident on ERG testing. Both patients show preservative of function in ring 1 only on multifocal ERG (very poor function), similar to earlier reports describing the clinical appearance to be more benign than the more severe functional abnormality detected with electrophysiology testing.

The retinal changes reported here bear some similarity to changes reported in hydroxychloroquine (HCQ) macular toxicity (‘flying saucer sign’ on OCT scanning). Neither of our patients received HCQ treatment for their MPS related arthropathy. The reported changes differ from typical HCQ toxicity by being symmetrical vertically around the fovea, rather than more prominent inferiorly, and by ERG features of rod-cone dystrophy rather than affecting rods and cones to a similar degree as occurs in advanced HCQ toxicity.

The cause of macular and retinal abnormality in patients with MPS I has not been definitively proven, but is thought to be secondary to GAG production by the RPE, failure of GAG metabolism leading to its accumulation, and subsequent cellular death occurring in phagocytic Müller cells and/or RPE. This is consistent with findings that gene therapy in murine models of MPS VII has been shown to reverse GAG accumulation in RPE and subsequent retinal degeneration. Bull’s eye maculopathy has not been definitively demonstrated to date in untreated MPS patients or in foveated animal models, using histopathological examination or OCT scanning. Wide phenotypic variation is well recognised in patients and families with the same genetic mutation in mucopolysaccharidoses similar to retinal degenerative disease, best exemplified by PRPH2 and ABCA4 and we hypothesise that the bull’s eye maculopathy may be a previously unrecognised phenotypic variant of retinal degeneration occurring in MPS I patients. Our younger patient does not have rod-cone dystrophy and follow-up will be important to determine whether the maculopathy is isolated or is associated with widespread dystrophy.

The cause of increased hyperreflectance in the region of the ELM, and whether it is intracellular or extracellular, is not known. It may represent undigested abnormal photoreceptor outer segments, although this is unlikely given that it is anterior to the ellipsoid line zone, or abnormal collagen deposition, which has been recently proposed to cause corneal clouding in MPS I-H.

Seok et al. proposed the material to be degraded GAG accumulating in Müller cells. The reason for deposition in the fovea with sparing of the remaining retina is not known. IDUA does not cross the blood-retina barrier. We propose that our patients with a clinically mild phenotype have some attenuated enzyme action in Müller cells allowing clearing of degraded GAG, but in the subfoveal location the increased number of photoreceptors results in a higher load of GAG and the limited enzyme capacity is overwhelmed. Also, foveal astrocytes have different structural and presumably functional properties to Müller cells; the enzymic activity is not known, but may be less in these more primitive retinal astrocytes. It is also possible that there is an inflammatory component to maculopathy from activated Muller cells, as activated microglia have been shown to be inflammatory in the cortex in murine models of MPS 1.

4. Conclusions

We report macular changes in patients with MPS I undergoing ERT, with clinical changes less significant than functional abnormality detected with ERG. This is the first report of a patient undergoing cataract surgery and the first report of multifocal ERG assessment. Further studies of untreated patients, and patients treated with both ERT and HSCT are needed to elucidate the nature of the macular changes and their relationship to treatment.

Patient consent

Both patients gave written consent to publish case details.

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Conflicts of interest

All authors have no financial disclosures: HGM, RCAS, GdJ.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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