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

Heather G. Mack [a, b, c, *], R.C. Andrew Symons [a, b], Gerard de Jong [b, d]

[a] Department of Surgery (Ophthalmology), University of Melbourne, Grattan St, Parkville, Victoria 3052, Australia
[b] Melbourne Health, 300 Grattan St, Parkville, Victoria 3052, Australia
[c] Walter and Eliza Hall Institute of Medical Research, 1G Royal Parade, Parkville, Victoria 3052, Australia
[d] Department of Medicine, University of Melbourne, Grattan St, Parkville, Victoria 3052, Australia

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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 hyperreflectant 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 α-L-iduronidase (IDUA),[1] of prevalence approximately 1 per 88,000 live births in Australia.[2] Gradual lysosomal accumulation of metabolites of IDUA glycosaminoglycan (GAG) substrates heparan and dematan 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. Interminable 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

* Corresponding author. 2/232 Victoria Parade, East Melbourne 3002, Australia.
E-mail address: hmack@eyesurgery.com.au (H.G. Mack).

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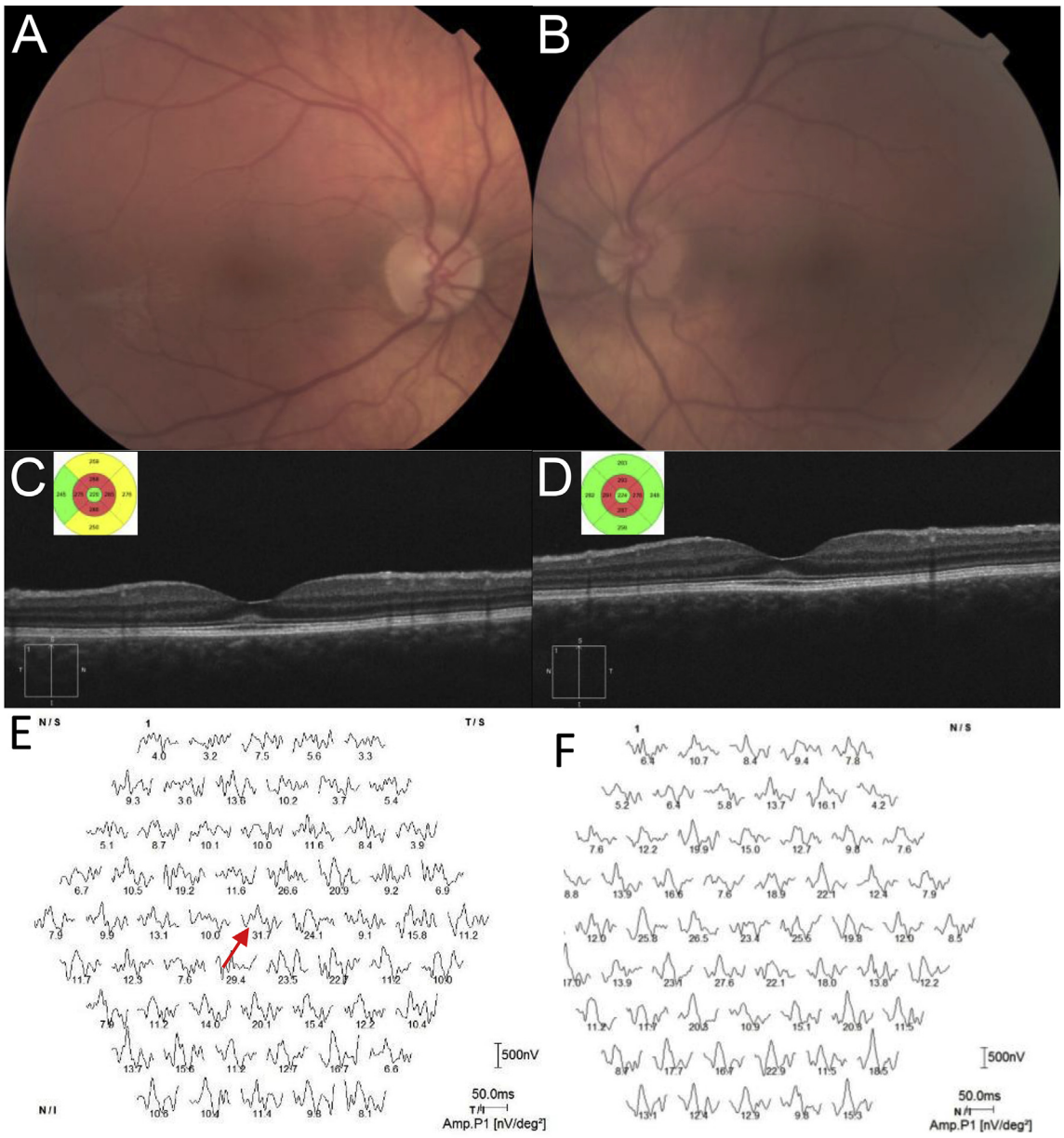

Fig. 1. A twenty-one year old male with mucopolysaccharidosis type I undergoing Laronidase enzyme replacement therapy.
A Color fundus photographs of the right and B left eye, showing slight foveal reddening, but no bull's' eye macular appearance. Images are blurred by corneal clouding. C Optical coherence 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 parafoveal 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.)

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 periphery[8,9] 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