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High-speed, Ultrahigh Resolution Optical Coherence Tomography of the Retina in Hunter Syndrome

Michael K. Yoon, MD, Royce W. Chen, BA, Thomas R. Hedges III, MD, Vivek J. Srinivasan, MS, Iwona Gorczynska, PhD, James G. Fujimoto, PhD, Maciej Wojtkowski, PhD, Joel S. Schuman, MD, and Jay S. Duker, MD

From New England Eye Center (MKY, RWC, TRH, IG, MW, JSD), Tufts-New England Medical Center, Tufts University, Boston, Massachusetts; the Department of Electrical Engineering and Computer Science and Research Laboratory of Electronics (VJS, IG, JGF, MW), Massachusetts Institute of Technology, Cambridge, Massachusetts; and UPMC Eye Center and the Eye and Ear Institute (JSS), Ophthalmology and Visual Science Research Center, Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

Abstract

A 42-year-old man with Hunter syndrome developed bilateral visual field loss. Visual field testing demonstrated bilateral ring scotomata that corresponded to areas of thinning seen on standard resolution optical coherence tomography. High-speed, ultrahigh resolution optical coherence tomography, capable of 3.5-micron axial resolution, showed a loss of photoreceptors outside the fovea and cystoid spaces within the inner nuclear, ganglion cell, and outer nuclear layers. These results were consistent with histopathologic features that have been reported previously in patients with Hunter syndrome. Optical coherence tomography could be used as a diagnostic modality to monitor patients with Hunter syndrome and to detect subclinical forms of disease.

INTRODUCTION

The lysosomal storage disease, Hunter syndrome or mucopolysaccharidosis type II, results from the X-linked inherited deficiency of the enzyme iduronate 2-sulfatase. Progressive dermatan sulfate and heparan sulfate accumulation in all tissues of the body leads to multiple systemic problems, including cardiac abnormalities, hepatosplenomegaly, and progressive deafness.

Ocular manifestations of Hunter syndrome include exophthalmos, hypertelorism, and pigmentary retinopathy. Unlike other lysosomal storage diseases, patients with Hunter syndrome typically exhibit clear corneas. Histopathologic and electron microscopic reports show retinal abnormalities similar to retinitis pigmentosa, including the loss of photoreceptors peripherally and the migration of retinal pigment epithelial pigment into the retinal layers.¹

The following case is an example of Hunter syndrome imaged with high-speed, ultrahigh resolution optical coherence tomography (OCT), which is capable of 3.5-micron axial resolution in the human eye² in comparison to 8- to 10-micron axial resolution of Stratus OCT (Carl Zeiss Meditec, Dublin, CA).³

Address correspondence to Thomas R. Hedges III, MD, Ophthalmology Department, Tufts-New England Medical Center, 750 Washington Street, Boston, MA 02111.

CASE REPORT

A 42-year-old man with Hunter syndrome was referred to our institution for evaluation of bilateral visual field loss. During the past few years, he had noticed difficulty seeing pedestrians while driving. On ophthalmic examination, his visual acuity was 20/30 in the right eye and 20/25 in the left eye. His corneas were clear bilaterally. Fundus examination showed normal-appearing retinas with no pigmentary changes. Both optic nerve heads were slightly crowded (Figs. 1A and 1B). Visual field testing (30-2 full-threshold test with the Humphrey Visual Field Analyzer [Carl Zeiss Meditec]) showed bilateral ring scotomata (Figs. 1C and 1D). Hertel exophthalmometry was 23 mm on the right and 21 mm on the left. Fluorescein angiography revealed choroidal folds in the left eye (Fig. 2A).

Multifocal electroretinography (Visual Evoked Response Image System; EDI, Inc., Burlingame, CA) showed a reduction in foveal responses bilaterally. There were decreased amplitudes throughout the 25° test area.

The retina was scanned with Stratus OCT. The retinal nerve fiber layer showed normal thickness around both optic nerve heads. Macular OCT showed generalized thinning of the retinas, most pronounced in the 3.0- to 6.0-mm ring around the foveae. In addition, small foveal and parafoveal cystoid spaces were seen in the inner retina bilaterally (Fig. 2B).

High-speed, ultrahigh resolution OCT showed several small hyporeflective cystoid spaces in the ganglion cell layer, inner nuclear layer, and outer nuclear layer bilaterally (Fig. 2C). Retinal thickness measurements were obtained using a radial scan protocol of 24 images centered on the foveola. Each image consisted of 1,500 axial scans. The outer retina was significantly thinned, especially outside a 1.5-mm diameter ring around the fovea (Fig. 3). The external limiting membrane was hyperreflective centrally, whereas the inner segment–outer segment photoreceptor junction could not be visualized beyond the parafovea. The hyperreflective band corresponding to the retinal pigment epithelium and photoreceptor outer segment tips appeared slightly thickened in the center bilaterally.

DISCUSSION

Several histopathologic and electron micrographic studies of the eye have been performed in patients with Hunter syndrome.^{1,4,5} All of these patients suffered from a more severe form of Hunter syndrome (mucopolysaccharidosis type IIa) in which death occurs before 35 years of age. Perhaps the most striking feature in these cases was photoreceptor degeneration with pigment migration into the retina.

This histopathologic appearance has been considered to be identical to retinitis pigmentosa despite the lack of characteristic findings on clinical examination, such as bone spicule pigmentation.⁶ One previous histopathologic report of Hunter syndrome described widespread loss of the retinal pigment epithelium and loss of the overlying photoreceptors.⁴ There have been no histopathologic descriptions of the retinas from patients with the mild form of Hunter syndrome.

Our patient experienced ocular symptoms typical of Hunter syndrome. He was both exophthalmic and hypertelorid, and he did not exhibit any corneal clouding. His pattern of visual field loss, with symmetric bilateral ring scotomata, suggested a significant degree of extrafoveal photoreceptor loss with central sparing. Consistent with previous electroretinographic reports, our patient had a mild bilateral reduction in foveal responses on multifocal electroretinographic testing.^{7,8}

Optic disc swelling has been described in a patient with Hunter syndrome in whom a histopathologic study revealed a grossly thickened posterior sclera with secondary compression of the optic nerve head.⁹ Our patient did have crowded discs on clinical examination and on retinal nerve fiber layer analysis with OCT. Furthermore, choroidal folds were seen in the left eye. These findings may have been secondary to infiltration of the sclera by mucopolysaccharides.

Standard resolution OCT showed a thinning pattern that corresponded to our patient's visual field impairments. Each of the nine sectors on the macular thickness map showed thinning compared with normal eyes,¹⁰ but the effects were most pronounced in the outer perifoveal ring. There also appeared to be small cystoid structures in the inner foveal and parafoveal retina of both eyes. Further localization of the cystoid spaces was not possible due to limited image resolution.

High-speed, ultrahigh resolution OCT provided more detailed images of the retina. The outer nuclear layer was attenuated, consistent with a previous histopathologic report of Hunter syndrome.⁴ There was marked thinning of the photoreceptor layer bilaterally. The external limiting membrane was surprisingly prominent in the foveal region, possibly reflecting the deposition of glycosaminoglycans. Peripherally, the photoreceptor inner segment–outer segment junction could not be distinguished from the retinal pigment epithelium, a sign of significant photoreceptor atrophy. Thickness measurements from the retinal pigment epithelium to the boundary of the photoreceptor inner segment–outer segment junction confirmed photoreceptor outer segment thinning, most pronounced outside a 1.5-mm diameter ring around the fovea. Beyond this ring, the photoreceptor inner segment–outer segment junction could not even be visualized.

A previous report using ultrahigh resolution OCT in patients with retinitis pigmentosa demonstrated similar atrophy of the photoreceptor layer in the extrafoveal retina.¹¹ In our case, the outer hyperreflective band corresponding to the retinal pigment epithelium and the tips of the photoreceptor outer segments appeared thickened centrally, possibly indicating retinal pigment epithelium hyperplasia, as described in a previous histopathologic study.⁵ Despite the mild clinical phenotype of our patient, these high-speed, ultrahigh resolution OCT findings correlated with the histopathologic findings of more severe forms of Hunter syndrome.

Several histopathologic reports of Hunter syndrome have shown multiple membranous lamellar vacuoles in the cytoplasm of retinal ganglion cells.^{1,4,5} With high-speed, ultrahigh resolution OCT, we were able to clearly localize several cystoid spaces to the inner nuclear, ganglion cell, and outer nuclear layers. The sizes of these spaces ranged from approximately 30 to 60 microns in depth and almost 100 microns in width. The composition of these spaces remains unknown, although they are likely intracellular collections of glycolipids that have been described histologically. We detected no evidence of vitreous bodies, cystic macular edema, or vitreoretinal interface abnormalities, all findings that have been shown by standard resolution OCT in one patient with Hunter syndrome.¹²

In July 2006, the U.S. Food and Drug Administration approved a new medication, idursulfase, as the first treatment for Hunter syndrome. In one study, this human enzyme replacement therapy has been shown to improve ambulation in patients who received weekly infusions.¹³ We do not yet know whether a correlation exists between macular thickness measured by OCT and treatment with idursulfase, but OCT could potentially identify structural markers for treatment response. Although the diagnosis of Hunter syndrome is made by detection of elevated levels of dermatan and heparan sulfate in the

urine and confirmed by detection of enzyme deficiency in fibroblasts, OCT might be used as a modality to detect subclinical disease.

High-speed, ultrahigh resolution OCT findings in our patient were consistent with histopathologic and ultrastructural features that have been reported previously in patients with Hunter syndrome. The OCT changes also correlated with visual field and electroretinographic testing. Because OCT is noninvasive, reproducible, and easy to perform, it could be used to monitor patients with Hunter syndrome, especially as new treatments become available.

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Figure 1.

(A, B) Color fundus photographs showing slightly crowded optic nerve heads. The posterior pole of the retina shows no pigmentary defects. (C, D) Automated perimetry showing ring scotomata in the right and left eye, respectively.

Figure 2.

(A) Fluorescein angiography of the left eye showing superotemporal choroidal folds with some staining of the temporal perifoveal region. (B) Horizontal Stratus OCT (Carl Zeiss Meditec, Dublin, CA) of the left eye revealing small foveal and parafoveal cystic spaces in the inner retina (arrow). There is marked thinning of the macula. (C) Horizontal high-speed, ultrahigh resolution OCT image of the left eye. There are several small hyporeflective cystic spaces in the ganglion cell layer (GCL), inner nuclear layer (INL), and outer nuclear layer (ONL). There is marked thinning of the photoreceptor layer. The external limiting membrane (ELM) appears thickened. IS/OS = photoreceptor inner segment/outer segment junction; RPE + PR OS = retinal pigment epithelium and reflective tips of the photoreceptor outer segments.

Figure 3.

Segmentation of high-speed, ultrahigh resolution optical coherence tomography (OCT) images of the right eye. (A) Fundus photograph demonstrating measurement areas. Circle diameters are 0.75, 1.5, 2.25, and 3.0 mm. (B) High-speed ultrahigh resolution OCT image. Bars represent retinal thickness (measured from the photoreceptor inner segment–outer segment junction to the vitreoretinal interface) and outer retinal thickness (measured from the photoreceptor inner segment–outer segment junction to Bruch's membrane). (C) False color map of full retinal thickness, measured from photoreceptor inner segment–outer segment junction to the vitreoretinal interface. The numbers represent average values in the annular regions. (D) False color map of outer retinal thickness, measured from the photoreceptor inner segment–outer segment junction to Bruch's membrane. The numbers represent average values in the annular regions. Measurements indicate significant photoreceptor outer segment thinning outside a diameter of 1.5 mm.