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Case Report Open Access

Fundus Autofluorescence and Enhanced Depth Imaging Spectral-Domain Optical Coherence Tomography in Hunter Syndrome-New Insights

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Abstract

Introduction: Hunter syndrome or mucopolysaccharidosis type II is a rare progressive multi-systemic disorder, caused by an abnormal storage of glycosaminoglycans (GAGs) in almost every cell type, including most ocular tissues [1,2]. Patients have a short life expectancy and ocular manifestations can be present early in the course of disease [1,2].

Purpose: To report the fundus autofluorescence and tomographic ocular findings in Hunter syndrome.

Methods: A 18-year-old male patient with Hunter syndrome with progressive nyctalopia was submitted to color fundus photography, blue fundus autofluorescence (FAF), fluorescein angiography (FA) and spectral domain optical coherence tomography with enhanced-depth imaging (EDI-SD OCT).

Results and discussion: Fundus examination and wide-field fluorescein angiogram revealed normal optic discs and bilateral pigmentary atrophic changes at the mid periphery with macular sparing. SD OCT revealed a retinal thinning due to external retinal atrophy affecting the photoreceptor layer beyond the parafoveal area. Although a prominent central external limiting membrane (ELM) was present, both the ellipsoid zone band and ELM could not be tracked beyond the central 2-mm and 2. 5 mm diameter ring, respectively. EDI-SD OCT revealed a highly irregular choroid, especially in its outer boundary, probably due to GAG scleral deposition. Blue FAF presented a symmetric hyperautofluorescent parafoveal ring that corresponded to the area where the ELM was present in the absence of the ellipsoid band. A mottled hyper/hypofluorescent pattern was present at the mid-peripheral retina. Scarce hyperautofluorescent dots were found in the left optic disc resulting from disc drusen which could result from axoplasmic flow disturbances due to GAGs scleral deposition.

Conclusions: To our knowledge this is the first report of fundus auto-fluorescence imaging in Hunter syndrome. We also report, for the first time, optic disc drusen in this disease. New imaging techniques can provide new insights for the understanding of this disease, and could potentially provide valuable biomarkers for treatment guidance.

Keywords: Hunter syndrome; Mucopolysaccharidosis type II; MPS II; Retinal degeneration; Fundus autofluorescence; Enhanced depth imaging; Spectral domain optical coherence tomography

Introduction

Hunter syndrome (Mucopolysaccharidosis type II; MPS II) is a rare X-linked recessive disease caused by an abnormal storage of glycosaminoglycans (GAGs) in almost every cell type [1,2]. It is caused by a deficiency in the lysosomal enzyme iduronate-2-sulphatase, involved in the degradative pathway of GAGs dermatan-sulphate and heparan-sulphate. This pathologic storage determines the clinical phenotype of these patients that suffer from growth retardation, multiple skeletal deformities, cardiomyopathy, severe airway obstruction, progressive loss of neurological functions and death usually around the first or second decade of life [1,2]. Recent enzyme replacement therapy using recombinant human I2S idursulfase has been showed to minimize GAGs' tissue storage, reducing its impact on end organ damage and increasing life expectancy [2,3].

Ocular manifestations can be present in an early stage of disease, however visual complaints other than nyctalopia are usually absent [1,2]. Histopathologic and ultrastructural examination has shown GAGs deposits in most ocular tissues [4]. Chronic edema of the optic disc due to increased pressure by scleral deposition of GAGs [5,6], uveal effusion [6,7], retinal detachment and epiretinal membranes [8] have been reported in these patients. A retinitis pigmentosa-like fundus appearance has been described, with loss of peripheral photoreceptors and retinal pigment epithelium (RPE) migration into the retinal layers [2,6,9].

Recent reports describe the optical coherence tomography (OCT) findings in Hunter patients, with a thinned macular retina, especially beyond the parafoveal area where photoreceptor atrophy was detected. Microcystoid like spaces in the ganglion cell, inner nuclear and outer nuclear layers have also been described [6,9,10].

Case Report

A 18-year-old male with Hunter syndrome was referred to our department due to progressive nyctalopia. His biochemical definitive diagnosis was made at 18 months of age by enzymatic assay. At presentation he had the characteristic clinical phenotype with macrocephaly, upper airway obstruction, mild pulmonary restriction, cardiomyopathy, hepatosplenomegaly and limitations of joint mobility. He was under idursulfase treatment for 7 years. His sole visual complaint was mild progressive nyctalopia. Visual acuity was 20/20 in both eyes. The anterior segment examination was unremarkable, presenting a clear cornea. Intra-ocular pressure was within normal values. Fundus examination (Figures 1) and wide-field fluorescein angiogram (Figures 2) revealed normal optic discs and bilateral pigmentary atrophic changes at the mid periphery of the retina that spared the central macula. A spectral-domain optical coherence tomography (SD-OCT) assessment (Figures 3) revealed the attenuation of the external retina beyond the parafoveal area. The ellipsoid zone band and external limiting membrane (ELM) could not be tracked beyond the central 2-mm and 2,5-mm diameter ring, respectively, however a prominent central ELM was bilaterally present. The outer nuclear layer was also absent beyond the central 3-mm diameter ring. No intra or sub-retinal fluid was detected, and the inner retina was unremarkable. Using the enhanced depth imaging (EDI) technique, a highly irregular choroid was observed, especially in its outer boundary, with an accentuated scleral-choroidal interface. Blue fundus auto-fluorescence (FAF) (Figures 4) presented a symmetric hyper-autofluorescent parafoveal ring, with an anatomic correspondence to the OCT transition zone (TZ), where the ELM was still present and the ellipsoid band absent. A mottled hyper/hypofluorescent pattern was present in the mid-periphery of both retinas. Scarce hyper-autofluorescent dots that corresponded to optic disc drusen were found in the left optic disc.

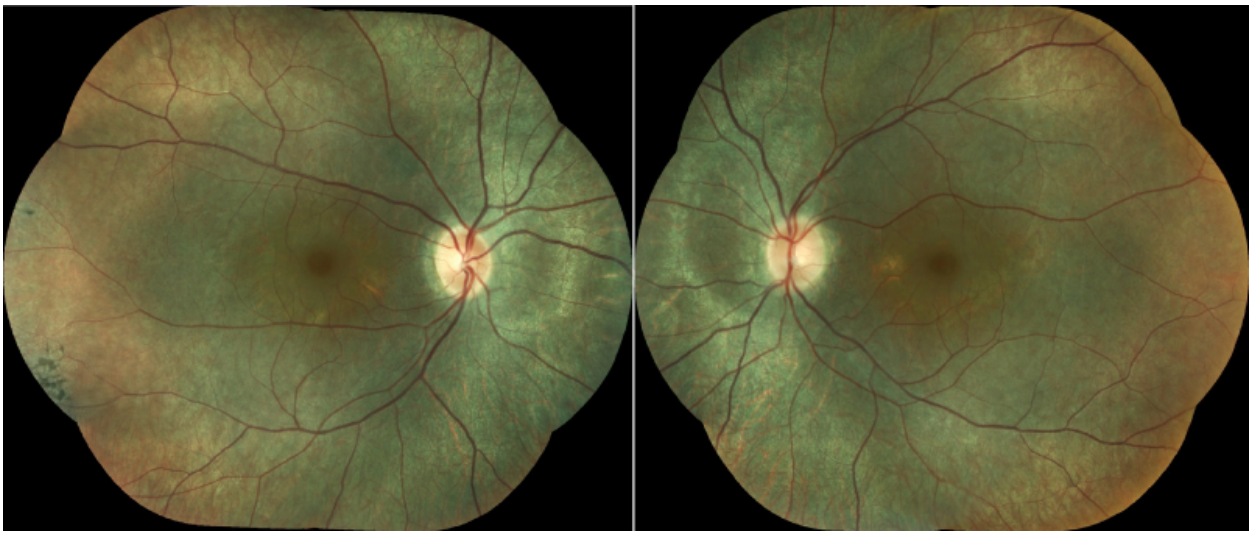

Figure 1: Fundus photography: Pan-fundoscopic fundus view showing mid-periphery retinal pigmentary changes, with a macular-sparing annular atrophy of the retinal pigment epithelium, allowing the visualization of choroidal vessels. Focal pigment clumping was evident temporal to the macula in OD. No changes in the optic disc or retinal vessels' caliber were evident.

Discussion

The short life span of patients with Hunter's syndrome makes long-term ocular assessment of dermatan sulfate and heparan sulfate deposition difficult [1,2]. Several histopathologic and ultrastructural studies reported GAGs deposition in most ocular tissues, especially in patients with a more severe form of disease [4,5]. A widespread loss of the retinal pigment epithelium and degeneration of the overlying photoreceptors has been described, in a similar pattern as in retinitis pigmentosa, despite the lack of the characteristic bone spicule pigmentation finding [4,6]. Retinal infiltration by GAGs has been proposed as a mechanism involved in the outer retinal changes [6]. The retinal degeneration observed in Hunter syndrome usually manifests with decreased peripheral vision and poor dark adaptation, but severe visual disturbance is not frequently reported [2].

Patients with less severe forms of disease, can be easily assessed by imaging techniques such as high-resolution SD-OCT with EDI and fundus autofluorescence. Contradicting reports regarding macular thickness have been published. Macular thickening has been described [2,6,7], but macular thinning due to photoreceptor outer segment's thinning was conversely reported [9-12]. Consistent with the latter reports, we found a significant retinal thinning in our patient, mainly caused by an atrophy of the external retina beyond the parafoveal area. The parafoveal outer nuclear layer was attenuated and the ellipsoid and ELM became undetectable beyond the central 2 and 2,5-mm central rings. The histopathologic published reports corroborate our findings, demonstrating a similar atrophy of the extrafoveal photoreceptor layer in Hunter patients. We also described an abnormally prominent central ELM, in accordance with other reports, probably resulting from the depositon of GAGs [9-13]. In fact, this intriguing feature has been described in early stage disease patients, that only showed thickening of the ELM with no other abnormal findings, suggesting that changes of the outer nuclear and photoreceptor layers precede RPE abnormalities [13]. The Müller cell is not only a glial cell-anchorage support but is also intrinsically involved in the maintenance of retinal regeneration and function. The progressive GAG deposition in Müller cells might induce functional abnormalities inducing secondary photoreceptor's degeneration [13].

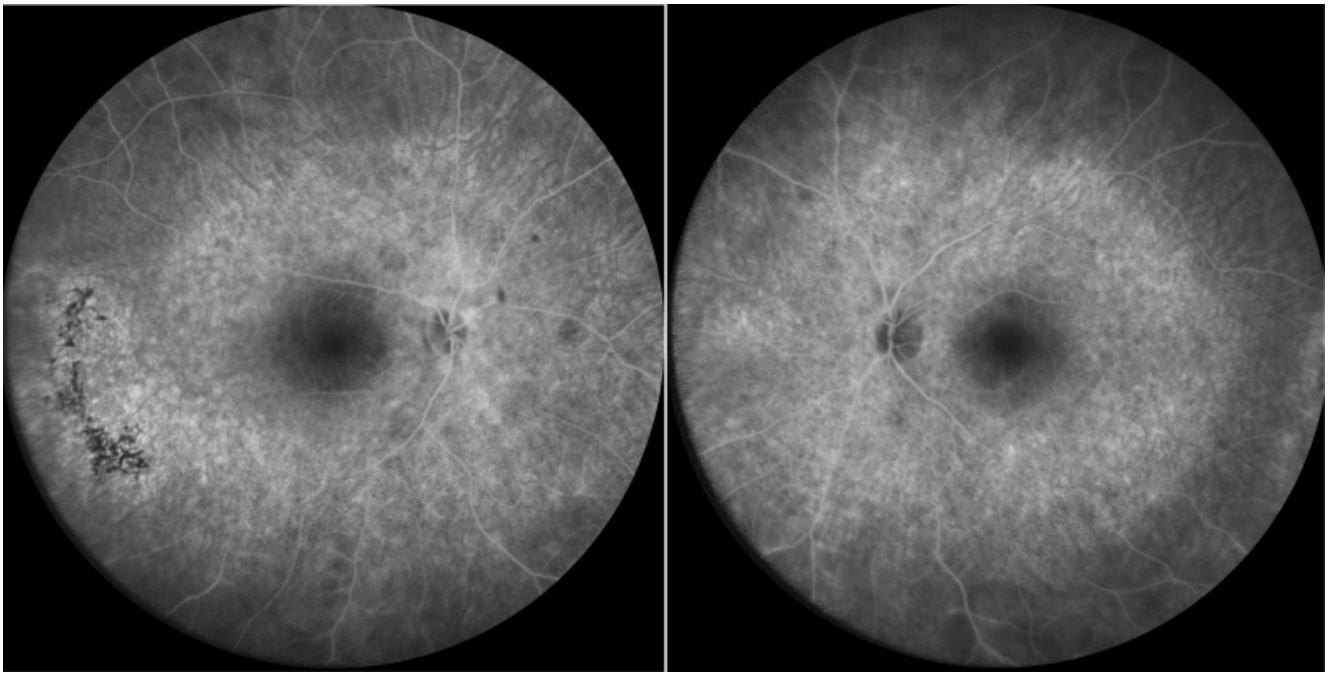

Figure 2: Wide-field fluorescein angiography: A mid-periphery hyperfluorescent ring was present resulting from outer retina and retinal pigment epithelium atrophy. No signs of leakage were found. Focal hypofluorescence caused by pigmentary clumping was present temporal to the macula in OD.

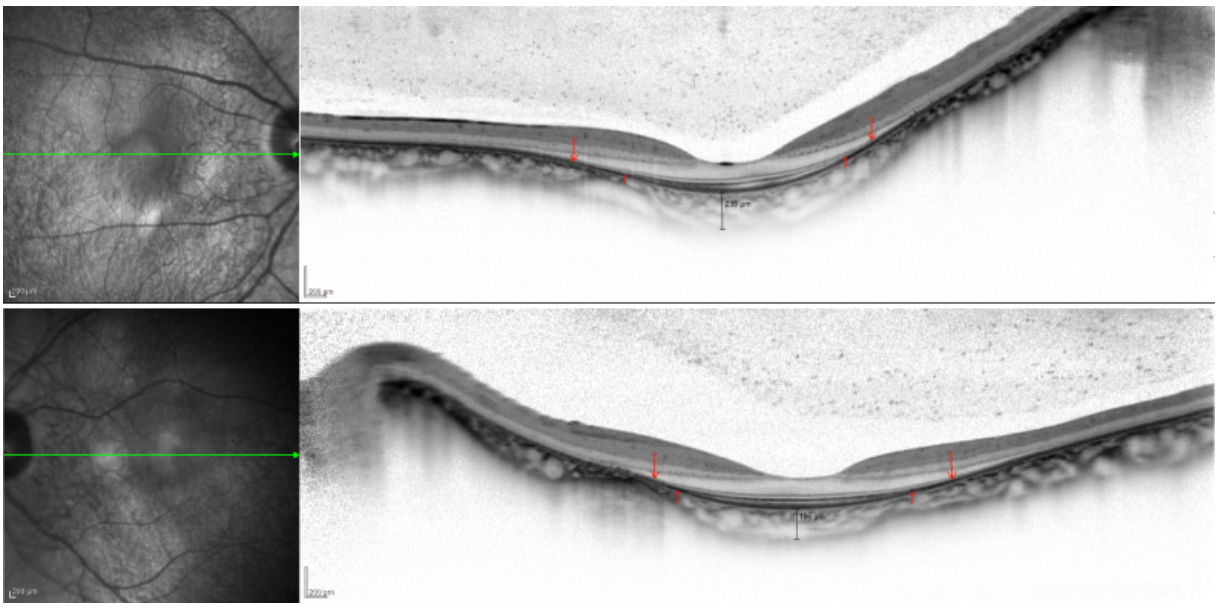

Figure 3: Spectral domain optical coherence tomography using enhanced depth imaging (EDI SD OCT) using the Spectralis device: The posterior boundary of the choroid presented a highly irregular contour, with no significant changes in its inner reflectivity. A bilateral symmetric parafoveal atrophy of the photoreceptor layer was detected, with a prominent central external limiting membrane (ELM). A circumferential transition zone (TZ) was found (between red arrows), where the ELM was still present (large head) but the ellipsoid zone (EZ) band was undetectable (small arrow). No changes were found in the inner retina or optic disc.

We found no previous reports on FAF findings in Hunter patients. Herein, we report for the first time a parafoveal ring with a morphometric anatomical correspondence to the OCT detected transition zone (TZ), where ELM was still present but no ellipsoid

band was found, probably meaning early functional rather than structural photoreceptor damage, affecting rods more than cones). The mottled hyperautofluorescent pattern we found in the mid-periphery could result both from the melano-lipofuscin extracellular or intracellular accumulation in either macrophages or RPE cells, while the small hypoautofluorescent dots could result from precocious RPE atrophy. Electroretinographic reports confirmed the evidence of retinal degeneration, presenting a pattern similar to rod-cone degeneration with more severely affected responses in rods than cones, outweighing the fundoscopic findings [6,14].

An uveal effusion syndrome has been described in Hunter patients by some other authors, speculating that it could result from the rupture of the external blood-retinal barrier or to an alteration of scleral permeability caused by diffuse GAG deposits in periocular tissues [7]. Although there is general consensus on the scleral infiltration with GAGs we only found one recent report on SD-OCT choroidal findings in MPS [9]. Our description of an irregular choroid correlates with their findings in 5 Hunter patients [9]. They also found focal choroidal thinning probably related to focal scleral thickening/protuberances.

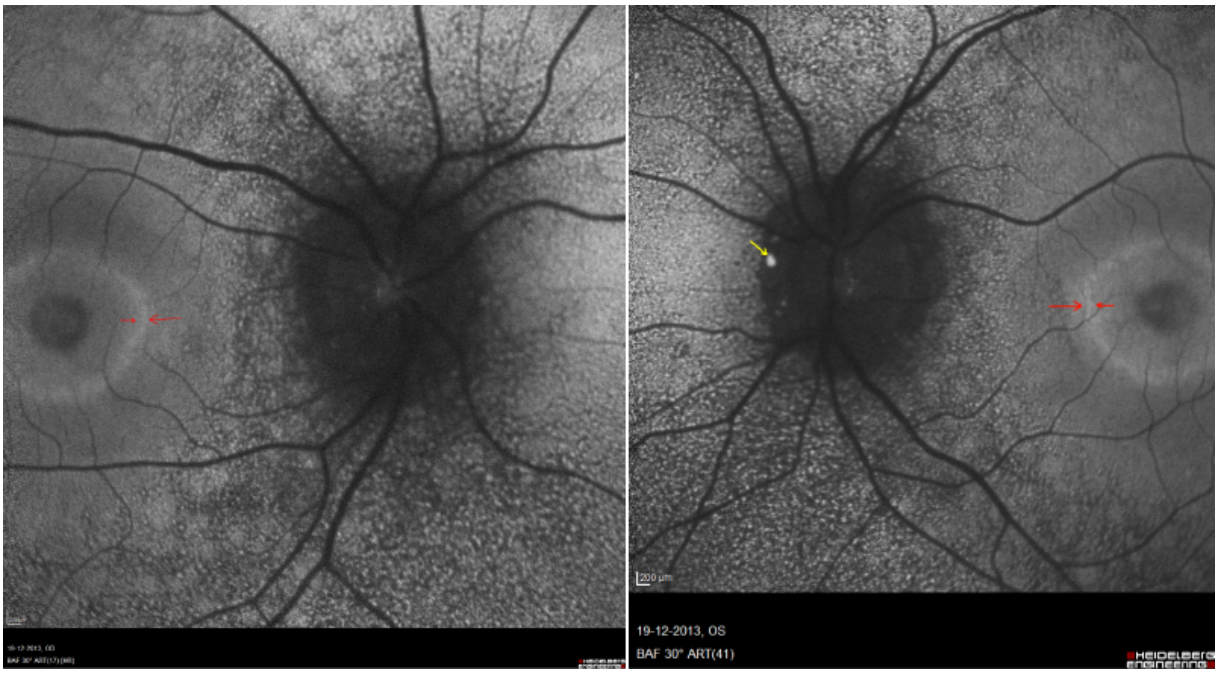

Figure 4: Blue fundus autofluorescence using the Heidelberg confocal scanning laser ophthalmoscope: A bilateral symmetric hyperautofluorescent parafoveal ring was detected (between arrows), with precise anatomic correspondence to the transition zone (TZ) described in the OCT. A mottled hyper/hypofluorescent pattern was present in the mid-periphery of the retina. Hyperautofluorescent dots were detected in the left optic disc (yellow arrow), corresponding to optic disc drusen.

Bilateral optic nerve swelling, without evidence of raised intracranial pressure, has been frequently described in these patients and it may be due to deposition of GAGs within the perioptic sclera, causing direct pressure on the optic nerve at the intrascleral level, as well as due to internal compression of the axons by the nerve septa, thickened by GAGs deposits [5]. This may result in axoplasmic flow disturbances, causing axoplasmic stasis and secondary gliosis, indicative of a reactive astrocytic response [5]. The optic disc drusen found on FAF could result from these neuro-axoplasmic flow disturbances. Optic disc drusen have also been described in other degenerative retinal disorders such as retinitis pigmentosa.

Conclusion

To our knowledge, this is the first report of the FAF pattern in Hunter patients, using a multimodal imaging approach. Herein, we also describe, for the first time, optic disc drusen in a Hunter patient, which could result from axoplasmic flow disturbances due to GAGs deposition.

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