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## Macular dystrophy in Heimler syndrome

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### Abstract

**Purpose**—To describe the retinal imaging findings in the index patient with Heimler syndrome (OMIM #234580).

**Design**—Non-interventional case report.

**Methods**—A 29-year-old woman with Heimler syndrome developed bilateral vision loss. Fluorescein angiography (FA), fundus autofluorescence (FAF), spectral domain optical coherence tomography (SD-OCT) and electroretinography (ERG) were performed to assess the retinal anatomy and function.

**Results**—FA showed mottling of the retinal pigment epithelium (RPE) in the posterior pole and periphery of the retina. FAF revealed hyper and hypoautofluorescent dots corresponding to the RPE mottling observed on FA. SD-OCT documented loss of the inner/outer segments boundary, and RPE thinning. ERG testing excluded generalized rod-cone dysfunction.

**Conclusion**—We report an adult-onset macular dystrophy in one of the previously reported patients with Heimler syndrome and hypothesize that this syndrome is probably an expression of a ciliopathy.

### Keywords

Amelogenesis imperfecta; Ciliopathy; Deafness; Heimler syndrome; Nail abnormalities; Retina

## INTRODUCTION

In 1991 Heimler described a new syndrome in a pair of siblings born to healthy and non-consanguineous parents.<sup>1</sup> They had enamel hypoplasia, nail malformations and deafness. In 1999 the third patient<sup>2</sup> a 12-year-old female, was found to have unilateral deafness, nail abnormalities and amelogenesis imperfecta of her teeth. Two other patients, 8- and 15-year-old female siblings, were reported in 2003<sup>3</sup> and presented with the same combination of

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hearing loss, nail abnormalities and amelogenesis imperfecta. The last two cases of Heimler syndrome were described in 2006.<sup>4</sup> We describe the previously unknown association of a macular dystrophy in one of the index patients with Heimler syndrome (patient #2).<sup>1</sup>

## CASE REPORT

The index case is now a 29-year-old woman with diminished visual acuity in both eyes for 1 year. She was born in the 39th week of an uneventful pregnancy. The patient had normal audiological tests until age 3 when she developed profound bilateral sensorineural hearing loss. At age 8, she was noted to have dental anomalies. Additional examination revealed Beau's lines on her toe nails which represent transverse depressions of the nail plates and leukonychia of the fingernails. She was otherwise in good health with no other pathological findings and her intellectual development had been normal.

One year before presentation the patient's ophthalmic examination was unremarkable. Both eyes were emmetropic and had a normal pupillary reaction without a relative afferent pupillary defect. At presentation the visual acuity was 20/200 in the right eye and 20/40 in the left eye. Ocular motility, slit-lamp biomicroscopy results, and intraocular pressures were unremarkable. Fundus examination of both eyes showed extensive "salt-and-pepper"-like mottling of the retinal pigment epithelium (RPE) involving the posterior pole and extending beyond the temporal vascular arcades (Figure 1). The optic disc appeared to be normal in both eyes.

Fluorescein angiography (FA) showed normal retinal circulation. There was mottled fluorescence throughout the posterior pole as well as non-leaking cystoid macular edema bilaterally. Fundus autofluorescence (FAF) showed hyper- and hypo-autofluorescent dots in the posterior pole and beyond the temporal vascular arcades sparing the fovea in both eyes (Figure 2). Spectral domain optical coherence tomography (SD-OCT) revealed multiple inner retinal cystoid spaces, thinning of the RPE, and loss of the inner segment/outer segment (IS/OS) junction in both eyes (Figure 3).

Full-field ERGs were performed with silver-impregnated fiber electrodes (DTL; Diagnosys LLC, Littleton, MA) using extended testing protocols incorporating the International Society for Clinical Electrophysiology of Vision (ISCEV) standards. The minimum protocol incorporates the rod-specific and standard bright flash ERGs, both recorded after a minimum of 20 min dark adaptation. Following 10 min of light adaptation, the photopic 30 Hz flicker cone and transient photopic cone ERGs were recorded. The scotopic rod specific ERG b-wave amplitudes (normal range:  $266.1 \pm 170.2 \mu\text{V}$ ), maximal ERG b-wave amplitudes (normal range:  $335 \pm 273.2 \mu\text{V}$ ), transient photopic ERG (normal range:  $178.8 \pm 116.9 \mu\text{V}$ ), photopic 30 Hz flicker ERG (normal range:  $131 \pm 82 \mu\text{V}$ ), and the pattern ERG (p50 normal  $>2 \mu\text{V}$ ) showed tracings within average (Figure 4). The multifocal ERG was abnormal with decreased sensitivity in the macular area in both eyes.

Because of hearing loss and "salt and pepper"-like retinopathy changes, laboratory tests for rubella (antibody tests IgM and IgG by Western blot), syphilis (VDRL and FTA-ABS), and Lyme disease (antibody tests IgM and IgG by Western blot) were ordered. However, the serology results for such diseases were negative. She was subsequently treated with acetazolamide 250 mg daily for her macular edema and her vision remained stable as of the last follow up (2 months after the treatment initiation).

## DISCUSSION

Our case presented with the systemic features seen in Heimler syndrome, namely sensorineural hearing loss, nail abnormalities and enamel hypoplasia with normal primary

dentition. The patient's retinal fundus examination revealed a "salt-and-pepper" mottling of the RPE in the posterior pole and beyond the vascular arcades with sparing of the fovea and the retinal periphery in both eyes. FAF showed hyper- and hypo-autofluorescent dots at the same topography, and SD-OCT revealed cystoid macular edema, thinning of the RPE, and loss of the IS/OS junction in both eyes. The normal full-field ERG excluded generalized retinal dysfunction. The patient's normal pattern ERG, nerve fiber layer within normal limits by OCT, and normal looking of optic discs reviewed previously by several seasoned clinicians indicate that there is absence of optic neuropathy. These features along with the absence of prior visual complaints and retinal abnormalities documented by several seasoned clinicians suggest an adult-onset macular dystrophy. The patient's ERG findings are not consistent with conditions that cause generalized retinal dysfunction such as Usher syndrome, retinitis pigmentosa and enhanced S-cone syndrome. Mitochondrial diseases, such as maternal inherited diabetes and deafness (MIDD), mitochondrial myopathy, lactic acidosis, and stroke-like episodes (MELAS), and Kearns-Sayre syndrome share "salt-and-pepper" pigmentary retinopathy and normal or mildly abnormal full-field ERG. However, the lack of extra-retinal features typically associated with these diseases such as diabetes, cardiomyopathy and encephalomyopathy make them improbable diagnoses in our case. Additionally, there is no electronegative ERG or implicit time delays on photopic 30 Hz flicker which makes inflammatory disease unlikely.

Heimler syndrome was hypothesized to be the consequence of a single gene involving derivatives of the ectoderm because the defects described have a common embryological source in the ectodermal tissue.<sup>1-4</sup> As retina also originates from the ectodermal tissue, the development of retinal degeneration could possibly coincide with deafness, nail abnormalities and amelogenesis imperfecta. The specific combination of IS/OS junction absence, hearing loss, nail abnormalities, and enamel hypoplasia seen in our patient could classify Heimler syndrome as a ciliopathy that is caused by dysfunction of the primary cilium with different phenotypes and overlapping disease expression.<sup>5,6</sup> Primary cilia take action as sensory organelles and as coordinators of a variety of signal transduction pathways. Ciliary defects could result in different human diseases that may reflect the involvement of cilia in such diverse sensory modalities and signaling pathways.<sup>7,8</sup> The wingless protein (WNT) and sonic hedgehog protein (SHH) represent the signaling pathways proven to be controlled by cilia.<sup>9</sup> Since SHH and WNT pathways are implicated in the formation of ectodermal elements such as the retina,<sup>10</sup> teeth,<sup>11,12</sup> nails<sup>13</sup> and auditory system<sup>14</sup> which are involved in our case, SHH and WNT signaling defects should be considered. Abnormal responses to SHH have been linked to ciliopathies associated with teeth and nail dysplasia such as Ellis-van Creveld syndrome.<sup>15</sup> Similarly, the enamel hypoplasia and nail malformations observed in Heimler syndrome could also be due to a SHH signaling malfunction. However, cilia are also related to other pathways such as platelet-derived growth factor and fibroblast growth factor<sup>16</sup> and the genetic defect in Heimler syndrome could be a result of other specific cilia protein abnormality. The categorization of a specific signaling pathway or protein defect in Heimler syndrome is complex given that most ciliopathies are genetically heterogeneous disorders and mutations of the same gene can cause widely varying phenotypes.

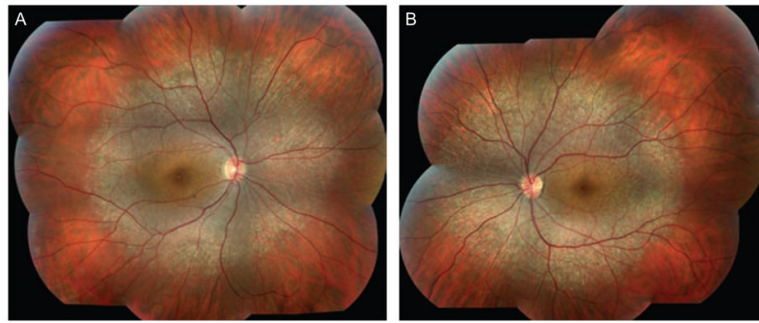
We report a unique case of Heimler syndrome associated with adult-onset macular dystrophy. Based on the presented case and a possible ciliopathy involvement we would recommend that patients presenting with the combination of hearing loss, nail abnormalities and amelogenesis imperfect undergo regular retinal examinations.

## Acknowledgments

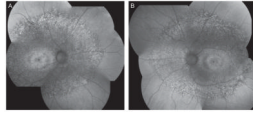
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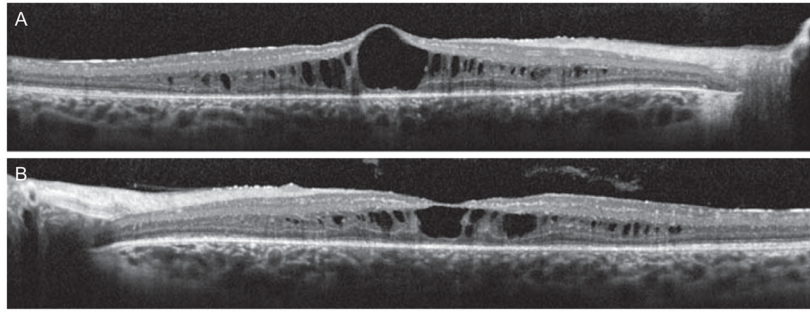
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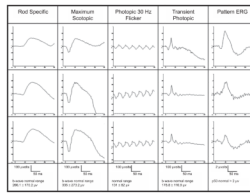
**FIGURE 1.**  
(A and B). Color fundus photographs of both eyes showing extensive “salt and pepper”-like mottling of the retinal pigment epithelium of the posterior pole and beyond the temporal vascular arcades.



**FIGURE 2.** (A and B). Fundus autofluorescence showed hyper- and hypo-autofluorescent dots in the posterior pole and beyond the temporal vascular arcades sparing the fovea in both eyes.



**FIGURE 3.** (A and B). Optical coherence tomography revealed multiple inner retinal cysts, thinning of the retinal pigment epithelium and disorganization of the inner segment/outer segment junction in both eyes.

**FIGURE 4.**

Full-field electroretinography (ERG) was normal with tracings within average in both eyes. The multifocal ERG showed decreased sensitivity in the macular area in both eyes.