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Early-Onset Stargardt Disease

Phenotypic and Genotypic Characteristics

Stanley Lambertus, MD,[1] Ramon A.C. van Huet, MD,[1] Nathalie M. Bax, MD,[1] Lies H. Hoefsloot, PhD,[2] Frans P.M. Cremers, PhD,[2,3] Camiel J.F. Boon, MD, PhD,[1,4] B. Jeroen Klevering, MD, PhD,[1] Carel B. Hoyng, MD, PhD[1]

Objective: To describe the phenotype and genotype of patients with early-onset Stargardt disease.

Design: Retrospective cohort study.

Participants: Fifty-one Stargardt patients with age at onset ≤10 years.

Methods: We reviewed patient medical records for age at onset, medical history, initial symptoms, best-corrected visual acuity (BCVA), ophthalmoscopy, fundus photography, fundus autofluorescence (FAF), fluorescein angiography (FA), spectral-domain optical coherence tomography (SD-OCT), and full-field electroretinography (ffERG). The *ABCA4* gene was screened for mutations.

Main Outcome Measures: Age at onset, BCVA, fundus appearance, FAF, FA, SD-OCT, ffERG, and presence of *ABCA4* mutations.

Results: The mean age at onset was 7.2 years (range, 1−10). The median times to develop BCVA of 20/32, 20/80, 20/200, and 20/500 were 3, 5, 12, and 23 years, respectively. Initial ophthalmoscopy in 41 patients revealed either no abnormalities or foveal retinal pigment epithelium (RPE) changes in 10 and 9 patients, respectively; the other 22 patients had foveal atrophy, atrophic RPE lesions, and/or irregular yellow-white fundus flecks. On FA, there was a "dark choroid" in 21 out of 29 patients. In 14 out of 50 patients, foveal atrophy occurred before flecks developed. On FAF, there was centrifugal expansion of disseminated atrophic spots, which progressed to the eventual profound chorioretinal atrophy. Spectral-domain OCT revealed early photoreceptor damage followed by atrophy of the outer retina, RPE, and choroid. On ffERG in 26 patients, 15 had normal amplitudes, and 11 had reduced photopic and/or scotopic amplitudes at their first visit. We found no correlation between ffERG abnormalities and the rate of vision loss. Thirteen out of 25 patients had progressive ffERG abnormalities. Finally, genetic screening of 44 patients revealed ≥2 *ABCA4* mutations in 37 patients and single heterozygous mutations in 7.

Conclusions: In early-onset Stargardt, initial ophthalmoscopy can reveal no abnormalities or minor retinal abnormalities. Yellow-white flecks can be preceded by foveal atrophy and may be visible only on FAF. Although ffERG is insufficient for predicting the rate of vision loss, abnormalities can develop. Over time, visual acuity declines rapidly in parallel with progressive retinal degeneration, resulting in profound chorioretinal atrophy. Thus, early-onset Stargardt lies at the severe end of the spectrum of *ABCA4*-associated retinal phenotypes. *Ophthalmology 2014;■:1−10 © 2014 by the American Academy of Ophthalmology.*

Stargardt disease (STGD1) is the most prevalent inherited juvenile-onset retinal dystrophy, with a mean age at onset of 15.2 years.[1,2] The inheritance pattern of STGD1 is autosomal recessive, and the disease is characterized by the presence of irregular yellow-white fundus flecks in the posterior pole.[2−4] Over time, the disease progresses to include macular depigmentation and chorioretinal atrophy. Typical STGD1 patients have normal—or near-normal—panretinal cone and rod function on full-field electroretinography (ffERG); however, progressive abnormalities in photopic and scotopic amplitudes have been reported.[5−7] Blockage of choroidal fluorescence (the so-called dark choroid sign) on fluorescein angiography is present in 80% of STGD1 patients.[8−10] The aforementioned yellow-white fundus flecks are hyperautofluorescent on fundus autofluorescence (FAF), presumably owing to an accumulation of lipofuscin fluorophores in the retinal pigment epithelium (RPE).[11,12] Spectral-domain optical coherence tomography (SD-OCT) can reveal changes in the outer nuclear layer, as well as photoreceptor loss, RPE abnormalities, and a general thinning of the retina.[13]

Mutations in the *ABCA4* gene have been associated with a spectrum of retinal diseases ranging from mild phenotypes (e.g., late-onset STGD1 with relatively preserved visual function) to severe, early-onset retinitis pigmentosa accompanied by a rapid loss of central and peripheral photoreceptors.[14−16] The *ABCA4* gene encodes the retinal-specific ATP-binding cassette transporter (ABCR).[17] *ABCA4* is expressed in both cones and rods. In rod cells, the ABCR protein is localized at the rim of the outer segment discs, where ABCR transports *all-trans*-retinal from the lumen of

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the outer segment disc to the cytoplasm of the photoreceptor cell.[18] The accumulation of *all-trans*-retinal—and its toxic derivatives—eventually results in the death of RPE cells and photoreceptor cells.[19–21] The *ABCA4* gene has high mutation heterogeneity; >700 distinct mutations have been identified to date, with a wide range of effects on ABCR protein function. A model to correlate the phenotype with the functional severity of the *ABCA4* mutation has been proposed.[22,23] According to this model, STGD1 results from mild to moderate ABCR impairment.

Among patients who are diagnosed with STGD1, the disease has remarkably wide clinical variability with respect to the general course of the disease, the retinal features, and the electrophysiologic findings.[5,8,14,15] Stargardt disease has both genetic and clinical overlap with cone–rod dystrophy, and this may cause confusion among general ophthalmologists; indeed, diagnosing STGD1 can be challenging at an early age. Therefore, obtaining an accurate description of the full spectrum of *ABCA4*-associated retinal dystrophies—including STGD1—is essential for providing appropriate patient counseling and adequate disease management, and may have important implications for selecting patients to participate in gene therapy trials. Although clinical features of STGD1 patients with a very young onset have been described in heterogeneous cohorts,[5,7,24,25] there is lack of studies concerning the natural history of these patients. Herein, we have provided a comprehensive description of the initial and longitudinal clinical and genetic characteristics of a large number of patients with early-onset Stargardt, which we defined as an age at onset ≤10 years.

Methods

Patients and Genetic Analysis

The database of the Department of Ophthalmology at Radboud university medical center (Nijmegen, The Netherlands) contains 426 patients with a clinical diagnosis of STGD1. For 258 of these patients, the *ABCA4* gene was analyzed by the Department of Human Genetics at Radboud university medical center (Nijmegen, The Netherlands). Known mutations were screened using the arrayed-primer extension microarray (Asper Biotech, Tartu, Estonia), and exon duplications and/or deletions were detected using multiplex ligation-dependent probe amplification (MRC-Holland P151/P152). If no mutations or only a single heterozygous mutation was identified, the exons and intron–exon boundaries were sequenced using the Sanger method to screen for mutations in the other allele. All identified mutations were confirmed using Sanger sequencing. In total, 199 patients contained ≥1 mutation in the *ABCA4* gene. Age at onset of disease was defined as the age at which symptoms were first noticed by the patient. If this information was not available, we used the patient's age at which he or she first visited an ophthalmologist.

In this study, we included 51 patients with an age at onset of ≤10 years and one of the following criteria: ≥2 *ABCA4* mutations (n = 37); 1 *ABCA4* mutation and the presence of yellow-white flecks (n = 7); or in the absence of *ABCA4* analysis, the presence of yellow-white flecks and either a dark choroid or an atrophic macular lesion (n = 7).

This study was approved by the Institutional Ethics Committee and was performed in accordance with the Declaration of Helsinki. All patients provided informed consent before giving a blood sample and receiving additional ophthalmologic examinations.

Clinical Evaluation

We defined the duration of disease as the time interval between the patient's age at onset (defined as described) and the age at the last visit. Best-corrected visual acuity (BCVA) was measured using a Snellen chart, then transformed into the logarithm of the minimum angle of resolution (logMAR) for subsequent analysis. A logMAR value of 1.9, 2.3, or 2.7 was assigned to the patient's ability to count fingers, detect hand movements, or perceive light, respectively.[26] Fundus characteristics were documented for 41 patients using fundus photography (Topcon TRC-50IX, Topcon Corporation, Tokyo, Japan). Fundus autofluorescence was performed in 32 patients using a confocal scanning laser ophthalmoscope (cSLO; Spectralis, Heidelberg Engineering, Heidelberg, Germany) fitted with an optically pumped solid-state laser (488-nm excitation).

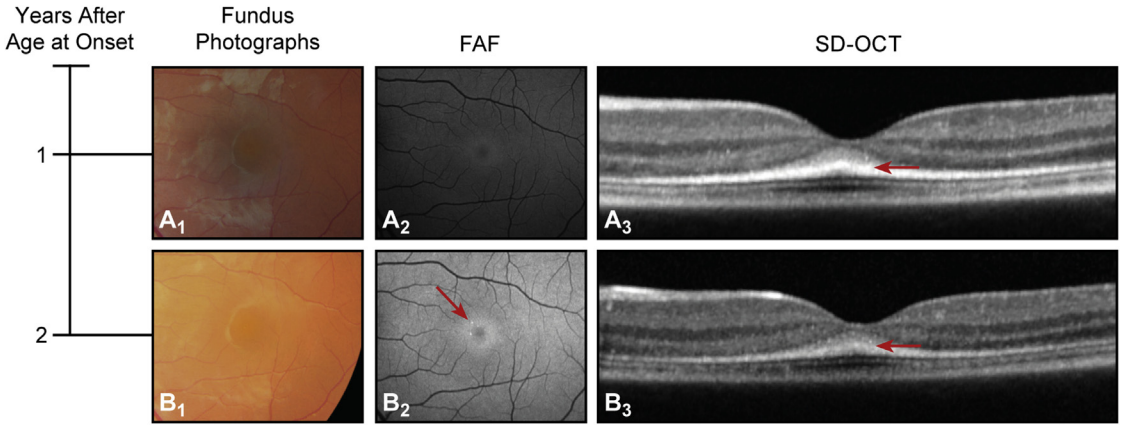

Figure 1. Retinal imaging of patient 4 (age at onset, 6 years; best-corrected visual acuity, 0.24 logarithm of the minimum angle of resolution; Snellen 20/35; *ABCA4* genotype: p.Thr983Ala and c.5461-10T>C (p.?)) at 7 ($A_{1,2,3}$) and 8 ($B_{1,2,3}$) years of age. Initially, only subtle foveal hyperautofluorescence was present (A_2); 1 year later, small parafoveal hyperautofluorescent flecks were present (the *arrow* in B_2), despite a lack of apparent abnormalities on ophthalmoscopy. Spectral-domain optical coherence tomography (SD-OCT) revealed foveal thickening of the band representing the external limiting membrane (the *arrows* in A_3–B_3). FAF = fundus autofluorescence.