The Ocular Phenotype in Primary Hyperoxaluria Type 1

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• PURPOSE: To investigate ophthalmic features in a large group of patients with primary hyperoxaluria type 1 (PH1) and to determine the relation between ocular involvement and systemic disease severity.

• DESIGN: Retrospective, cross-sectional, multicenter study of the OxalEurope Registry Network.

• METHODS: Sixty-eight patients with PH1 were included. Infantile PH1 was diagnosed in 12 patients, and non-infantile PH1 was diagnosed in 56 patients (17 with end-stage renal disease). Ophthalmic examination included best corrected visual acuity (BCVA) testing and multimodal retinal imaging, including fundus photography and optical coherence tomography (OCT). In selected cases, fundus autofluorescence imaging was performed.

• RESULTS: All eyes (n = 24) of infantile PH1 patients revealed severe retinal alterations and oxalate deposits, including macular crystals and hyperpigmentations (n = 9, 38%), and subretinal fibrosis (n = 15, 63%) with (n = 7, 47%) or without (n = 8; 53%) associated chronic retinal edema. In 9 eyes (38%, all with subretinal fibrosis), BCVA was significantly reduced (<20/50 Snellen equivalent). In contrast, all eyes (n = 112) of patients with non-infantile PH1 had a BCVA in the normal range (median, 20/20). Only 6 patients with non-infantile disease (11%, all with end-stage renal disease) showed mild, likely PH1-related retinal features. These deposits appeared as focal hyperreflective subretinal lesions on OCT imaging and were hyperautofluorescent on autofluorescence images.

• CONCLUSIONS: Severe ocular alterations occur in infantile cases, whereas mild or no ocular alterations are typical in non-infantile PH1 patients. The natural history of (sub)retinal oxalate deposits, the pathogenesis of subretinal fibrosis, and exact factors influencing the overall severity of ocular disease manifestation remain to be determined. (Am J Ophthalmol 2019;206:184–191.

PRIMARY HYPEROXALURIA TYPE 1 (PH1) IS A RARE autosomal recessive inherited disorder of the glyoxylate metabolism caused by mutations in the *AGXT* gene.[1–6] The resulting lack, dysfunction, or mislocalization of the liver-specific peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT) leads to an increased production of the insoluble metabolic end product oxalate, which is mostly eliminated by the kidneys.[1–3] The overproduction of oxalate results in calcium oxalate crystal formation primarily in the kidneys, and a chronic inflammatory process induced by oxalate itself ultimately leads to renal failure.[7,8] Once a calcium oxalate plasma threshold of 30 μmol/L is exceeded and/or kidney function is reduced (glomerular filtration rate, <40–50 ml/min/1.73 m^2), the risk for non-renal oxalate deposits increases (e.g., in the bone, eye, and myocardium).[7]

Two disease manifestations of PH1 can be differentiated: 1) infantile oxalosis with end-stage renal disease (ESRD) in the first weeks of life, resulting in a significantly increased morbidity and mortality and 2) the more common non-infantile form with ESRD by 20–30 years of age or even later in life.[6,7] Variable disease expression may occur in those with the same underlying genotype, even within families.[6,7,9] Genetic and environmental modifying effects have been suggested,[6,9] but the exact explanation for this phenotypic heterogeneity remains unknown.

Conservative management of PH1 can delay but not prevent decline in renal function and includes pyridoxine (vitamin B6) supplementation, hyperhydration (>3 L/m^2/day), and calcium oxalate crystallization inhibitors (e.g., potassium citrate).[7] Even if dialysis is performed, oxalate continues to accumulate in the

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body. Hence, combined or sequential liver-kidney transplantation provides the only causative treatment for advanced disease, which is particularly challenging in young children with infantile oxalosis.[7] Currently, novel therapeutic approaches are being explored, including substrate reduction by RNA interference as well as gene therapy.[10,11] To study therapeutic efficacy, valid outcome parameters are needed.

Previous reports described retinal oxalate deposits in the neuroretina, the retinal pigment epithelium (RPE), and the sub-RPE space of PH1 patients, indicating that these could serve as disease biomarkers for longitudinal studies.[12–31] Furthermore, ophthalmologic screening, including multimodal high-resolution ophthalmic imaging with in vivo visualization of subtle phenotypic alterations, could be used to identify individuals with early-onset systemic deposits. This might help to identify patients who may be more likely to require an aggressive therapeutic strategy. However, a better understanding of the retinal phenotype and its association with systemic disease would be needed before considering retinal changes as disease biomarkers in PH1 patients.

Even though diverse ocular abnormalities were previously described in patients with PH1,[12–31] detailed reports of retinal manifestations using high-resolution imaging for visualization of subtle phenotypic changes are sparse. The purpose of this study was to investigate ocular phenotype in the largest group of PH1 patients reported to date and to determine its relation to systemic disease severity.

METHODS

• **PATIENT SELECTION:** This retrospective, cross-sectional, multicenter study followed the tenets of the Declaration of Helsinki. Informed written consent of the OxalEurope Registry Network was obtained from each patient, which included eye examinations. Reported patient data were collected between December 2013 and December 2018 at 3 academic centers: The University of Bonn, Germany; Amsterdam UMC, The Netherlands; and the University Medical Center Hamburg-Eppendorf, Germany. Diagnosis of PH1 was confirmed by genetic testing in 66 patients and by liver biopsy in 2 patients (#1, #30; Table S1).

• **OPHTHALMIC EXAMINATION:** All patients underwent a clinical examination, including best corrected visual acuity (BCVA) testing, slit-lamp examination with a detailed evaluation of the conjunctiva and lens, dilated indirect ophthalmoscopy, and multimodal retinal imaging. In infants, the Preferential Looking Test was performed instead of BCVA examination. Retinal imaging included, in most cases, fundus photography (Zeiss Visucam; Zeiss, Oberkochen, Germany), fundus autofluorescence, near-infrared reflectance images with a confocal scanning laser ophthalmoscope (Spectralis HRA+OCT or HRA2; Heidelberg Engineering, Heidelberg, Germany), and spectral-domain optical coherence tomography (OCT) imaging (Spectralis HRA-OCT or DRI OCT Triton; Topcon, Tokyo, Japan). Fluorescein angiography was performed in selected cases. A history with regard to ocular diseases and visual symptoms was obtained from each patient.

• **NEPHROLOGY EXAMINATION:** A general medical history was obtained from each patient, which included the age of onset and type of initial symptoms, disease progression, as well as transplantation history. Furthermore, the estimated glomerular filtration rate, plasma oxalate levels, and pyridoxine responsiveness were determined.

• **STATISTICAL ANALYSIS:** Statistical analysis was performed using GraphPad Prism v6.0 for Windows (GraphPad Software, La Jolla, California, USA). Visual acuity and age at examination were compared among the 3 phenotypic infantile PH1 subgroups by the analysis of variance test followed by the Tukey test for pairwise comparison of groups if a significant difference was shown by analysis of variance. Unpaired *t*-tests were used to compare age progressed to ESRD and age in ESRD.

RESULTS

SIXTY-EIGHT PH1 PATIENTS (31 FEMALE; 46%) FROM 61 FAMilies were included in this study, of whom 12 (18%) presented with infantile PH1. All infantile cases had progressed to ESRD at a median (range) of 0.4 years (0.1–0.6). Eleven (92%) of the infantile cases had received combined or sequential liver-kidney transplantation before examination, and 1 was on the waiting list at the time of examination. In the non-infantile oxalosis patients (n = 56), median (range) age at first symptom and diagnosis was 4.3 years (0.1–57.8) and 8.4 years (0.3–62.8), respectively. Seventeen patients (30%) in the non-infantile group had progressed to ESRD, of whom 6 (11%) had received combined or sequential liver-kidney transplantation. Further demographic and laboratory features are shown in Table S1.

• **RETINAL PHENOTYPE OF INFANTILE PH1 PATIENTS:** The median age at the time of the ophthalmic examination was 10 years (range, 0.9–17 years). Median BCVA was 20/50 (range, 20/500–20/32; n = 20 eyes of 10 patients). In the 2 youngest patients, only the Preferential Looking Test was available.

On fundus color images (examples in Figure 1), 9 eyes (38%) showed pronounced crystalline oxalate deposits

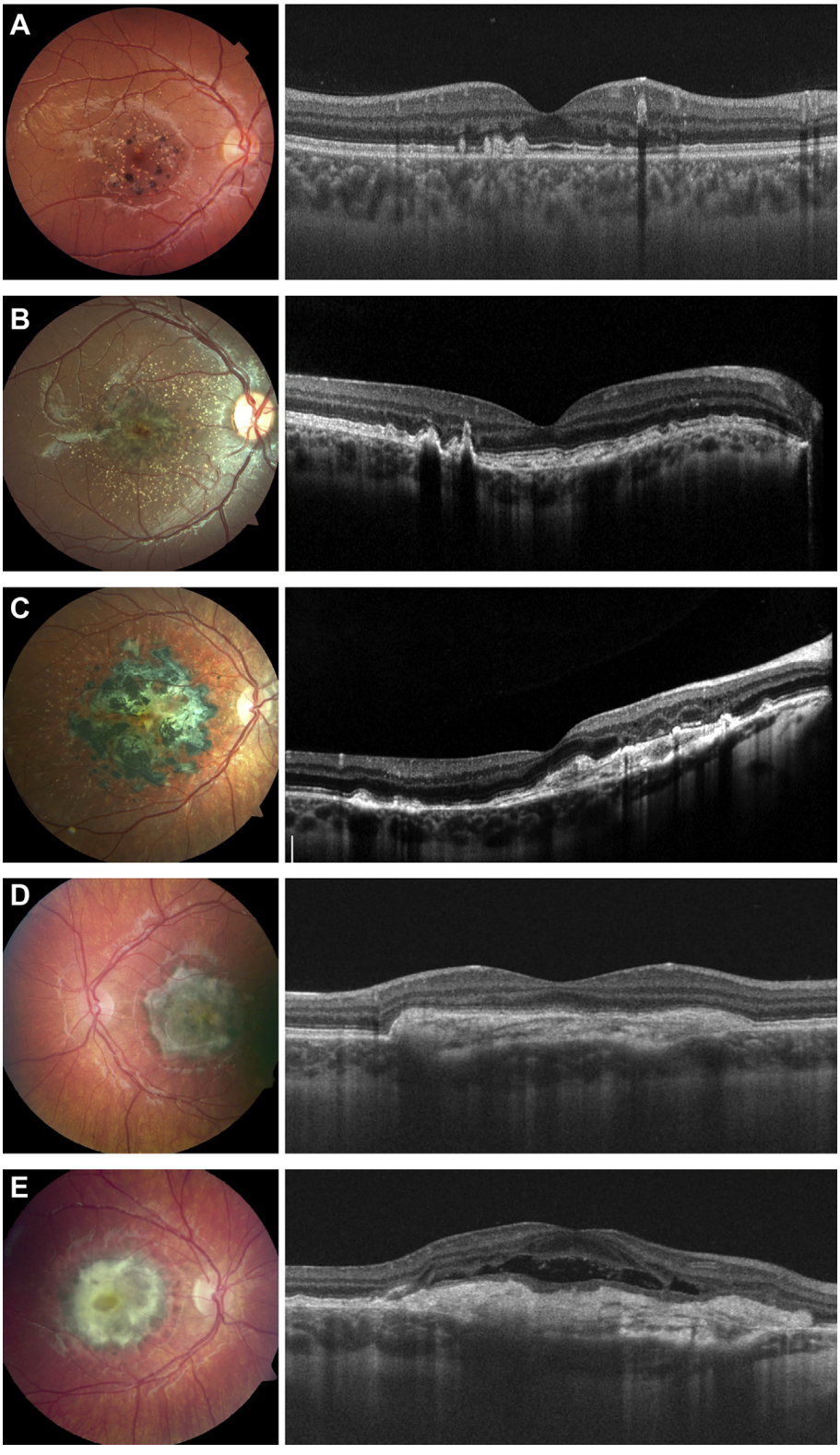

FIGURE 1. Oxalate deposits and severe retinal alterations in patients with infantile PH1. Color fundus photograph (left) and OCT (right) images. (A-C) Macular crystals that appear as small focal subretinal hyperreflective lesions on OCT imaging. (B, C) The OCT correlate for the rather confluent macular hyperpigmentations was an irregular thickening of the RPE band. (D, E) OCT imaging may also reveal subretinal hyperreflective material reminiscent of tissue seen in patients with fibrosed neovascular membranes. The overlying neurosensory retina was either relatively preserved (D) or disrupted by intraretinal and/or subretinal fluid (E). (A) = #3, 17 years; (B) = #11, 7 years; (C) = #12, 6 years; (D, E) = #7, 9 years.

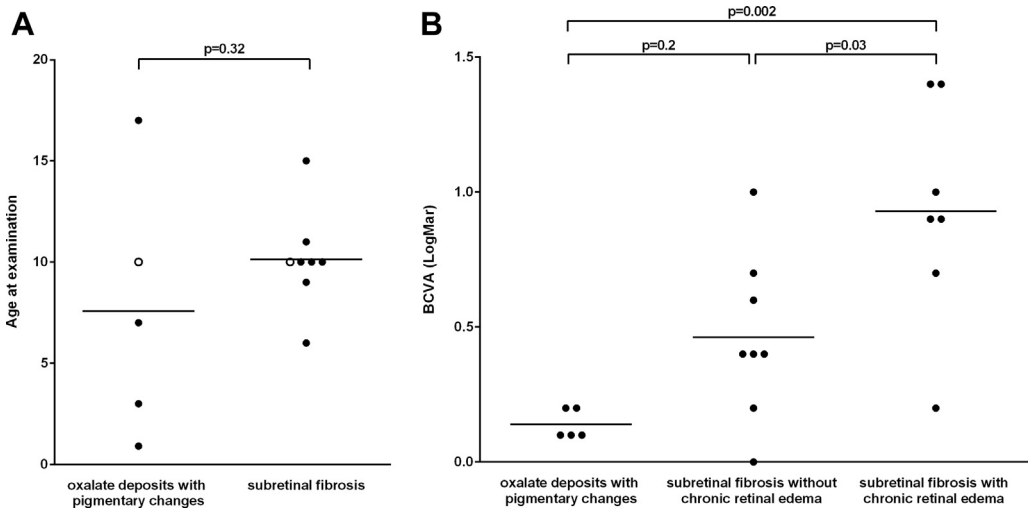

FIGURE 2. Age at examination and visual acuity in patients with infantile PH1. (A) Patients without subretinal fibrosis tend to be younger than those with subretinal fibrosis. The circle represents a patient with 1 eye in each group. (B) BCVA differed between the 3 phenotypic subgroups.

with pigmentary changes, and 15 eyes (63%) presented with macular subretinal fibrosis with (n = 7) or without (n = 8) associated intraretinal and/or subretinal fluid on OCT imaging. If present, subretinal fibrosis was observed bilaterally except in 1 patient, and patients without fibrosis tended to be younger than patients with fibrosis (Figure 2A). BCVA differed between the 3 subgroups ($P = 0.002$), with overall best BCVA in eyes without subretinal fibrosis (all ≥20/32; logMar, 0.2) and worst BCVA in those with subretinal fibrosis and intraretinal and/or subretinal fluid (Figure 2B). Eyes with subretinal fibrosis but BCVA ≥20/50 (logMar, 0.4; n = 6) showed foveal sparing or a relatively preserved foveal photoreceptor layer despite fovea-involving subretinal fibrosis.

On OCT images, macular crystals appeared as small focal subretinal hyperreflective lesions (Figure 1A–C). Focal hyperpigmentations correlated to focal dome-shaped elevated RPE alterations but were also seen as intraretinal hyperreflective lesions (Figure 1A). The OCT correlate for the rather confluent macular hyperpigmentary changes as shown in Figure 1B was an irregular thickening of the RPE band, and, within this area, crystalline deposits appeared reduced or absent on color and OCT images. In patients with more pronounced macular changes, OCT imaging may reveal subretinal hyperreflective material reminiscent of tissue seen in patients with fibrosed neovascular membranes (Figure 1C–E). The overlying neurosensory retina was relatively preserved with either diffuse thinning or focal atrophies of the outer retina (Figure 1C, D), or it was more severely altered with subretinal and/or intraretinal fluid (Figure 1E). Of note, crystalline deposits could be absent even outside the area of subretinal fibrosis, at an eccentricity (i.e., around the vascular arcades) where these were often observed in patients without or with less severe fibrotic changes. Retinal hemorrhages or exudates were not observed in this cohort.

• **RETINAL PHENOTYPE OF NON-INFANTILE PH1 PATIENTS:** The median age at ophthalmic examination in non-infantile PH1 patients (n = 56) was 23 years (range, 2–67 years). None of the patients reported visual problems or reduced visual acuity, and median BCVA was 20/20 (range, 15/20–30/20). For a 2-year-old patient, only the Preferential Looking Test was available. One patient (#19) was treated with topical brimonidine and brinzolamide for glaucoma.

Only 6 (11%) of the 56 patients with non-infantile PH1 showed small, drusen-like retinal changes that were interpreted as crystallized oxalate. These deposits appeared as focal hyperreflective subretinal lesions on OCT imaging and were hyperautofluorescent on autofluorescence images (autofluorescence was available in 4 patients; Figure 3A, B). The few observed deposits either had the same morphologic characteristics as in non-infantile cases (Figure 3A) or seemed to be located underneath the RPE and then appeared more yellowish-orange and less well defined (example in Figure 3B). These 6 patients had progressed to ESRD at 46.2 ± 16.5 years (mean ± standard deviation; compared to 15.6 ± 12.4 years in those with ESRD without oxalate deposits; $P = 0.002$) and were in ESRD for 2.6 ± 4.3 years (mean ± standard deviation; compared to 5.6 ± 6.7 years in those in ESRD without oxalate deposits; $P = 0.38$). Most (5/6) of these patients were older than 40 years of age at the time of examination (Figure S1A). Furthermore, 2 of these 6 patients were in ESRD, but their calcium oxalate plasma levels did not exceed the presumed plasma threshold for oxalate deposits of 30 μmol/L (Figure S1B). Of note, these

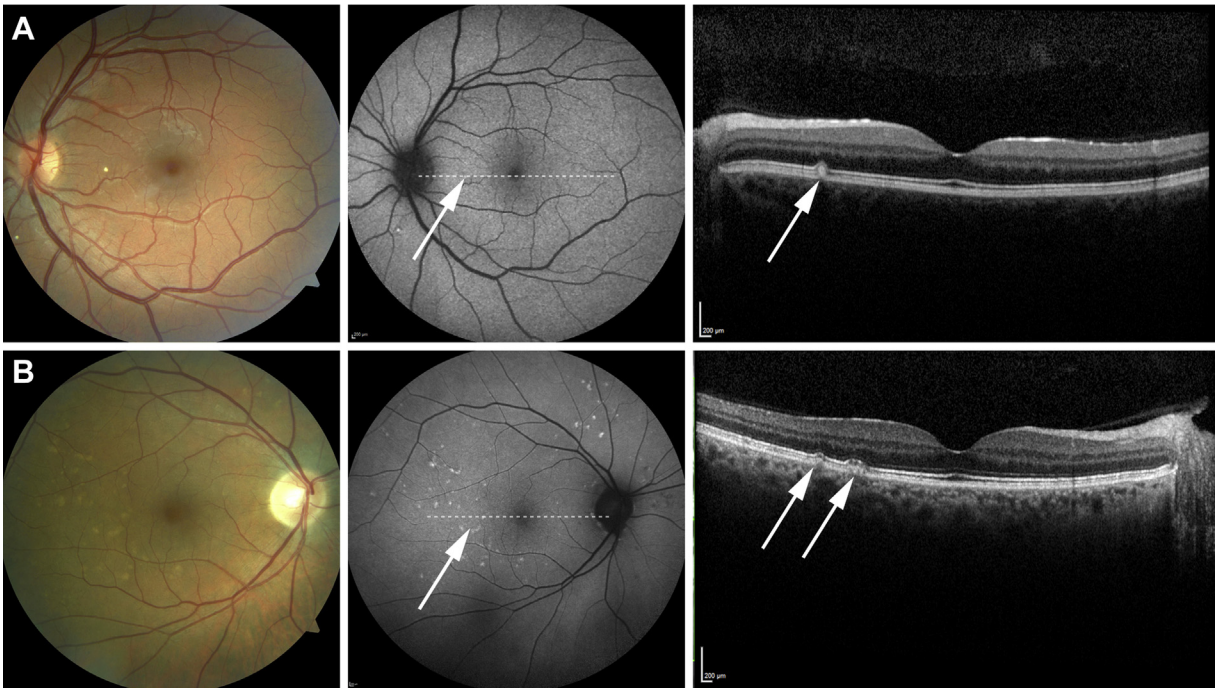

FIGURE 3. Retinal alterations identified in patients with non-infantile PH1. Color fundus photograph (left), fundus autofluorescence (middle), and OCT (right) images of small, drusen-like retinal changes (oxalate deposits). The dashed line indicates the position of the respective OCT scan. The arrow indicates oxalate deposits on the respective position on fundus autofluorescence and OCT imaging. (A) = #30, 27 years; (B) = #23, 59 years.

patients were treated with vitamin B6 supplementation for several years, and their genotype (homozygous c.508G>A mutations) is known for its vitamin B6 responsiveness that can lead to normal or near-normal endogenous oxalate production. In general, there was no obvious association between the retinal alterations and plasma oxalate levels in this cohort, in which most patients already had intensive treatment or a history of hepatorenal transplantation (Table S1, Figure S1B).

In 7 patients (13%, 10 eyes) funduscopy revealed small, faint yellowish or pigmentary changes that were not detected on OCT examination and could not reliably be classified as oxalate deposits. Most (5/7) of these patients were younger than 40 years. Only 2 patients were in ESRD (for 1.4 or 7.4 years), and the calcium oxalate plasma threshold was exceeded in 3 patients at the time of examination (Figure S1).

The remaining 43 non-infantile PH1 patients (77%) showed no retinal oxalate deposits, and 9 of these patients had ESRD. Three of these 43 patients (7%, 5 eyes) presented with mild retinal hemorrhages, which were interpreted to be related to hypertensive crisis or hemodialysis. One of them also revealed peripheral hyperfluorescent deposits and perivascular sheathing with mild leakage on angiography (Figure S2).

• **ANTERIOR SEGMENT INVOLVEMENT IN PH1:** Due to the retrospective and multicenter study design and a focus on retinal alterations, no reliable conclusion on the frequency of anterior segment involvement can be drawn for the entire cohort, particularly because no standardized photography of the anterior segment of the eye was performed. Documented alterations included mild crystallizations in the conjunctiva in 7 patients (Figure S3), cataract in 8 patients (posterior subcapsular, n = 4; cortical, n = 4, of which 3 were older than 45 years and had previous steroid treatment), focal lens abnormalities in 3 patients, and pseudophakia in 1 patient.

DISCUSSION

BASED ON THIS STUDY OF 68 PH1 PATIENTS, INCLUDING 12 infantile cases, and a review of previous published work, 2 patterns of ocular involvement in PH1 can be distinguished (Figure 4): 1) patients with infantile PH1 usually present with severe retinal abnormalities, resulting in a variable degree of vision loss already at a young age; 2) in sharp contrast, most patients with non-infantile PH1 reveal a normal retina, and only few—all in ESRD and mostly

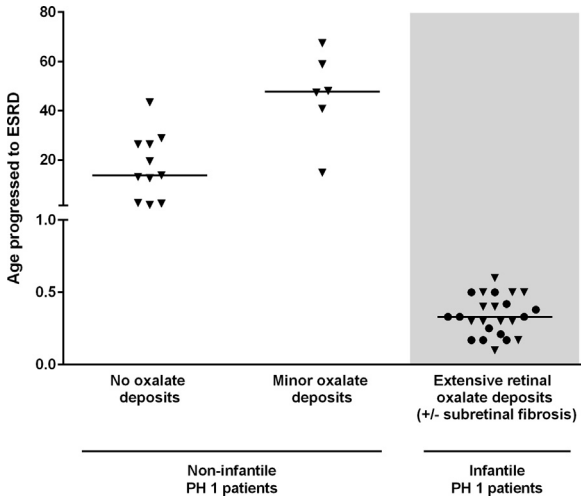

FIGURE 4. Retinal disease severity depends on systemic disease severity in PH1. All cases with extensive retinal oxalate deposits with or without subretinal fibrosis are patients with infantile PH1, which is characterized by early onset of ESRD. Triangles represent cases reported in this study; black circles represent patients reported with sufficiently detailed medical history in previous literature. Note that only non-infantile patients who progressed to ESRD are shown. Two previously published patients with presumed non-infantile PH1 and extensive retinal changes are not included because of insufficient detail of their reported medical history.[17,19]

over 40 years of age—show mild retinal changes that do not significantly affect visual function.

• **PATHOPHYSIOLOGIC CONSIDERATIONS CONCERNING RETINAL PHENOTYPE IN PH1:** The pronounced oxalate deposition in infantile PH1 patients might be explained by the usually very high oxalate levels before transplantation compared to non-infantile PH1 patients. Additional explanation for the severe retinal phenotype only in infantile PH1 may include a particularly low threshold for subretinal oxalate deposits at a young age (e.g., due to an immature and more susceptible choroid-Bruch's membrane-RPE complex) and/or a more severe tissue response to such deposits. In non-infantile PH1 patients, the apparently higher susceptibility for mild retinal changes in older patients is counterintuitive and may need to be investigated further in independent cohorts.

In infantile PH1, the sequence of events leading to the late disease stage with macular subretinal fibrosis has not yet been characterized in detail. Based on a review of the literature, including histopathologic studies, and taking our findings into account, the following manifestations potentially occur in succession:

1) *Crystalline deposits*. Histopathologic studies of early cases indicate that oxalate crystallization first occurs below the RPE.[21] These calcium-oxalate deposits may then interrupt the RPE layer[19–22] and, as demonstrated by OCT imaging, may extend into the outer retina.[12,30] In support of an early, mild disease manifestation, crystalline deposits were seen in the youngest infantile cases and the few non-infantile patients with mild retinal changes.
2) *Focal hyperpigmentations*. The likely histologic correlate is hyperplasia and hypertrophy of RPE cells, triggered by calcium oxalate.
3) *Diffuse macular hyperpigmentation*. Continued secondary RPE cell proliferation may lead to a confluent, disorganized RPE multilayer. During this process, oxalate deposits might be encased and/or cleared.
4) *Subretinal fibrosis*. The exact pathophysiology resulting in formation of a subretinal collagenous layer remains to be determined, but it may involve chronic inflammation and/or RPE cell metaplasia. Subretinal fibrosis may be associated with accumulation of intraretinal and/or subretinal fluid that, over time, may contribute to chronic degenerative retinal changes.

Such suggested disease course is reflected by a recently proposed grading of macular changes in PH1.[13]

A better understanding of the exact pathogenesis of subretinal fibrosis will be important for determining the need for frequent retinal examinations in patients with infantile PH1. If the fibrotic process would mainly involve a tissue response to oxalate deposits in the subretinal space, no frequent monitoring would be needed owing to the current lack of ophthalmologic therapeutic options. Secondary choroidal neovascularizations have rarely been reported but have not been implicated directly in the formation of the characteristic fibrosis in PH1.[19,28] If neovascular processes would also play a relevant role, intravitreally injected inhibitors of vascular endothelial growth factor would be available. In this case, frequent monitoring for early detection of treatable disease stages would be fundamentally important to reduce related structural retinal damage and functional decline. At present, retinal screening, including OCT imaging, should be considered as a standard imaging procedure in patients with infantile PH1.

• **RETINAL EXAMINATION AT THE ADVENT OF NOVEL THERAPEUTIC APPROACHES:** Meaningful and reliable outcome measures are required for clinical trials as novel therapeutic modalities are on the horizon, such as RNA interference targeting upstream glycolate oxidase, or further downstream liver-specific lactate dehydrogenase A to deplete the substrate for oxalate synthesis, or *Oxalobacter formigenes* interacting with colonic epithelium and inducing colonic oxalate secretion.[10,11,32–35] Monitoring PH1-associated retinal changes would be a noninvasive option, since multimodal, high-resolution ophthalmic imaging enables in vivo visualization of the smallest phenotypic alterations and longitudinal quantification of

retinal pathology over time. However, due to the heterogeneity of ocular manifestations with only rare and mild changes in non-infantile cases, and the yet unknown rate of dynamic changes over time, the benefit of retinal biomarkers has to be further elucidated. If early normalization of oxalate levels would reduce the risk of developing fibrosis in infantile PH1 patients, this might be an outcome measure in interventional trials due to the significant and permanent effect on visual function. In this regard, it is also important to understand whether there is a point of no return where future fibrotic changes would be inevitable. Of note, most (9/10) infantile cases with subretinal fibrosis examined in this study previously underwent an early liver-kidney transplantation and thereafter revealed comparatively normal plasma oxalate concentrations. Longitudinal studies will be needed for further clarification.

Moreover, it is unknown if therapeutic interventions resulting in lower oxalate plasma concentration would consistently result in stabilization or even reversal of ocular oxalate deposits and how long such resorption would take. Derveaux et al[13] observed no regression of crystals at the level of the RPE in 1 patient during 5.5-year follow-up after successful combined kidney-liver transplantation. However, other studies demonstrated reversal of retinal oxalate deposition after kidney transplantation or increased frequency of dialysis, and the lack of crystals outside the subretinal fibrosis as well as within the area of diffuse pigmentation (Figure 1) indicates existence of mechanisms for clearing oxalate deposits from the subretinal space.[16,29,30,36] Thus, more longitudinal data especially after transplantation are necessary to evaluate mobilization of insoluble oxalate pools and whether retinal changes may decrease the same way as it has been described, e.g., in bone involvement.

• **LIMITATIONS:** The relatively young age of the patients in this cohort does not allow conclusions to be drawn regarding long-term outcomes. Moreover, the retrospective, cross-sectional study design precludes confirmation of the hypothesized sequence of disease and does not allow conclusions to be drawn on the rate of change depending on baseline findings. Moreover, the plasma oxalate levels included in this study represent values at a given moment in time, which may account for a poor correlation of the retinal disease severity with plasma oxalate levels, as the latter may not be representative of the previous disease course.

CONCLUSIONS

IN THIS PATIENT COHORT REPRESENTATIVE FOR THE HETerogeneous PH1 population, we showed that severe ocular alterations usually occur in infantile PH1 cases, whereas mild or no ocular alterations are typical in non-infantile PH1 patients. In light of emerging interventional strategies, longitudinal studies will be needed to determine factors influencing the onset of crystallization, if retinal oxalate deposition is reversible especially after hepatorenal transplantation, to elucidate mechanisms leading to formation of subretinal fibrosis, and if monitoring retinal PH1-related changes may indicate disease progression or therapeutic efficacy.

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