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Ophthalmic Manifestations of ROSAH (Retinal Dystrophy, Optic Nerve Edema, Splenomegaly, Anhidrosis, and Headache) Syndrome, an Inherited NF κB–Mediated Autoinflammatory Disease with Retinal Dystrophy

Laryssa A. Huryn, MD[1], **Christina Torres Kozycki, MD**[2,3], **Jasmine Y. Serpen, BA**[1], **Wadih M. Zein, MD**[1], **Ehsan Ullah, PhD**[1], **Alessandro Iannaccone, MD, MS**[4], **Lloyd B. Williams, MD, PhD**[4], **Lucia Sobrin, MD, MPH**[5], **Brian P. Brooks, MD, PhD**[1], **H. Nida Sen, MD**[1], **Robert B. Hufnagel, MD, PhD**[1], **Daniel L. Kastner, MD, PhD**[2], **Shilpa Kodati, MD**[1]

[1]National Eye Institute, National Institutes of Health, Bethesda, Maryland.

[2]National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland.

[3]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland.

[4]Duke Eye Center, Duke University School of Medicine, Durham, North Carolina.

[5]Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.

Abstract

Purpose: We aimed to characterize the ocular phenotype of patients with ROSAH (retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and headache) syndrome and their response to therapy.

Correspondence: Laryssa A. Huryn, MD, National Eye Institute, National Institutes of Health, 10 Center Drive, Building 10, 10D45, Bethesda, MD 20892. laryssa.huryn@nih.gov.

Author Contributions:

Conception and design: Huryn, Kozycki, Kastner, Kodati

Analysis and interpretation: Huryn, Kozycki, Serpen, Zein, Ullah, Iannaccone, Williams, Sobrin, Brooks, Sen, Hufnagel, Kastner, Kodati

Data collection: Huryn, Kozycki, Zein, Brooks, Sen, Hufnagel, Kastner, Kodati

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Overall responsibility: Huryn, Kozycki, Serpen, Zein, Ullah, Iannaccone, Williams, Sobrin, Brooks, Sen, Hufnagel, Kastner, Kodati

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HUMAN SUBJECTS: Human subjects were included in this study. The Institutional Review Board at National Institutes of Health approved the study. All research complied with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and adhered to the tenets of the Declaration of Helsinki. All participants or guardians provided informed consent.

No animal subjects were included in this study.

Design: Single-center observational case study.

Participants: Eleven patients with a diagnosis of ROSAH syndrome and mutation in *ALPK1* were included.

Methods: Patients with molecularly confirmed ROSAH syndrome underwent ophthalmic evaluation, including visual acuity testing, slit-lamp and dilated examinations, color fundus and autofluorescence imaging, fluorescein angiography, OCT, and electrophysiologic testing.

Main Outcome Measures: Visual acuity, electrophysiology, fluorescein angiography, and OCT findings.

Results: Eleven individuals (6 female and 5 male patients) from 7 families ranging in age from 7.3 to 60.2 years at the time of the initial evaluation were included in this study. Seven patients were followed up for a mean of 2.6 years (range, 0.33–5.0 years). Best-corrected visual acuity at baseline ranged from 20/16 to no light perception. Variable signs or sequelae of intraocular inflammation were observed in 9 patients, including keratic precipitates, band keratopathy, trace to 2+ anterior chamber cells, cystoid macular edema, and retinal vasculitis on fluorescein angiography. Ten patients were observed to show optic disc elevation and demonstrated peripapillary thickening on OCT. Seven patients showed retinal degeneration consistent with a cone–rod dystrophy, with atrophy tending to involve the posterior pole and extending peripherally. One patient with normal electroretinography findings and visual evoked potential was found to have decreased Arden ratio on electrooculography.

Conclusions: Leveraging insights from the largest single-center ROSAH cohort described to date, this study identified 3 main factors as contributing to changes in visual function of patients with ROSAH syndrome: optic nerve involvement; intraocular inflammation, including cystoid macular edema; and retinal degeneration. More work is needed to determine how to arrest the progressive vision loss associated with ROSAH syndrome.

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Keywords

Cone–rod dystrophy; Optic disc elevation; Syndromic retinal dystrophy; Uveitis; Vasculitis

ROSAH (**R**etinal dystrophy, **o**ptic nerve edema, splenomegaly, **a**nhidrosis, and **h**eadache) syndrome is a rare autosomal dominant disorder characterized by, as the name suggests, retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and headache.[1,2] The disease is caused by heterozygous missense variants in alpha kinase 1 (*ALPK1*: c.710C→T [p.Thr237Met] and c.761A→G [p.Tyr254Cys]), a gene encoding an innate immune receptor for bacterial sugars including the lipopolysaccharide precursor ADP-beta-D-mannoheptose.[1–6] However, the mechanisms underlying changes in visual function in this unique multisystem disease remain poorly understood.

Recently, ROSAH-associated variants have been demonstrated to cause a gain of function, leading to enhanced constitutive activation of the ubiquitous proinflammatory nuclear factor κB (NF-κB) pathway.[6] Consistent with innate immune activation, patients with

ROSAH syndrome can show signs and symptoms of systemic inflammation, including recurrent fever, fatigue, arthritis, esophagitis, and elevated inflammatory markers such as C-reactive protein and plasma tumor necrosis factor α. However, ROSAH syndrome also has been associated with several clinical features not classically attributed to inflammation, including hypoplasia of dental enamel, short dental roots, and inability to sweat or lactate. Furthermore, Alpk1 has been shown to localize to the base of primary cilia, leading the initial authors who described ROSAH syndrome to speculate that the disease may be a form of ciliopathy.[2] The first known description reported a mother and 2 daughters with an inherited disorder consisting of splenomegaly, cytopenias, and vision loss.[3] The ophthalmic features included early onset optic disc edema with gradual progressive vision loss, particularly central, and color vision compromise in the setting of a cone dystrophy or cone–rod dystrophy (CORD) and vascular leakage on fluorescein angiography. These patients showed variable degrees of intraocular inflammation in the form of anterior chamber or vitreous cell on examination. Further study of 4 additional, unrelated families identified the molecular cause of this ocular multisystem disorder as an *ALPK1* missense pathogenic variant, and the syndrome was named ROSAH. Decreased vision associated with optic nerve edema was noted as the most common initial feature of ROSAH.[2] Low-grade ocular inflammation and a cone-rod pattern of visual impairment are among the ophthalmic features of the syndrome, with the visual impairment becoming severe by the third decade of life.[2] A subsequent report of 2 Chinese patients with the *ALPK1* c.710C→T, p. T237M (NM_001102406) mutation in the setting of splenomegaly, intermittent fever, anhidrosis, ophthalmic findings, and elevated serum tumor necrosis factor α levels was published.[1] Ophthalmic findings in these patients included anterior and posterior segment uveitis, vitreous hemorrhage, optic disc edema, intraretinal hemorrhage, macular edema, retinal neovascularization, cystic changes in the retina, retinoschisis, and retinal degeneration. Discontinuities of the retinal pigment epithelial layer and disruption of the ellipsoid zone were observed on OCT, as well as reduced scotopic responses on full-field electroretinography (ffERG).[1]

Thus, to understand the main factors contributing to vision loss and the natural history of ophthalmic disease better in patients with ROSAH syndrome, we identified a cohort of 11 individuals at varying stages of the disease and performed deep ocular phenotyping to characterize and define further systematically the manifestations of this rare disease, as well as to report on the results of treatment in a subset of patients.

Methods

Eleven individuals from 7 families with a diagnosis of ROSAH syndrome and mutation in the *ALPK1* gene were examined at the National Eye Institute's ophthalmology clinic as part of studies of the National Human Genome Research Institute (ClinicalTrials.gov identifier, NCT00001373) and the National Eye Institute (ClinicalTrials.gov identifier, NCT02471287). All participants or guardians provided written informed consent. The study was approved by the Institutional Review Board of the National Institutes of Health and adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act.

Medical and ophthalmic history were reviewed. Best-corrected visual acuity, manifest or cycloplegic refractions, color vision, and visual field were measured in patients who could participate in testing. Anterior segment examination as well as dilated funduscopy were performed for each patient. Axial length (IOLMaster; Carl Zeiss Meditec AG), corneal staining, Schirmer testing, and intraocular pressure were measured in patients who could cooperate. Data were obtained from the baseline visit, when available, or the next visit at which the specific testing was performed. OCT (Cirrus HD-OCT [Carl Zeiss Meditec] or Spectralis OCT [Heidelberg Engineering]), color and fundus autofluorescence (Topcon and Optos ultra-widefield retinal imaging devices), and ultra-widefield fluorescein angiography (Optos) were performed when possible. Two graders (S.K. and L.A.H.) independently reviewed optic disc images for presence of disc elevation and peripapillary and vascular changes. In those patients who could cooperate with the examination, International Society for Clinical Electrophysiology of Vision standard ffERG images, electro-oculography images, and visually evoked potentials were recorded using a commercial electrophysiology system (LKC).[7,8] Descriptive statistics were used for analysis of results.

Results

Eleven patients from 7 families with ROSAH syndrome were evaluated, ranging in age from 7.3 to 60.2 years at the time of the initial evaluation. Six patients were female, and 5 patients were male; 9 patients self-reported as non-Hispanic White, and 2 patients self-reported as Hispanic White. Patients 1 through 10 were found to have *ALPK1* NM_025144.4:c.710C→T [p.Thr237Met], whereas patient 11 was found to have a novel variant in *ALPK1*, namely NM_025144.4:c.761A→G [p.Tyr254Cys] (Table 1). Patients 1 through 4 represent 3 generations of one family, and patients 8 and 9 represent 2 generations of another family; the remaining patients are unrelated. Demographics, molecular results, and clinical features are outlined in Table 1; clinical data were obtained from the baseline visit, and electroretinography data were obtained from first visit at which the specific testing was performed.

Best-corrected visual acuity at the baseline visit ranged from 20/16 to no light perception in the right eye (mean, 0.60 logMAR [Snellen equivalent, 20/80] for those with measurable vision on the Snellen chart) and 20/16 to no light perception in the left eye (mean, 0.75 logMAR [Snellen equivalent, 20/112] for those with measurable vision on Snellen chart). Three eyes of 2 patients had visual acuity of no light perception; in 2 patients, this likely was secondary to advanced retinal dystrophy, and in 1 patient, this was likely the result of a retinal detachment. On review of records, the retinal detachment was diagnosed as exudative 7 years prior; however, on our evaluation, extensive proliferative vitreoretinopathy was noted, consistent with a rhegmatogenous component. Of the 2 eyes with light perception vision, 1 patient experienced an episode of acute angle-closure glaucoma, and in the other patient, it was attributed to advanced degenerative changes. Additionally, one other patient had a history of acute angle closure. One nonverbal patient with cerebral palsy and a history of multiple ventriculoperitoneal shunts had very limited ability to participate in vision testing and had visual acuity of least light perception, although her family described an ability to pick up high-contrast objects. Three patients noted photophobia at the time of evaluation, whereas 3 patients reported nyctalopia. Mean spherical equivalent when

available was +1.33 diopters (D) in the right eye (range, −0.75 to 5.00 D) and +1.58 D in the left eye (range, −0.75 to 5.00 D; n = 5). For patients who were able to complete axial length measurements at the time of baseline or subsequent evaluation, mean axial lengths were 21.70 mm in the right eye (range, 20.53–22.38 mm; n = 5) and 21.62 mm in the left eye (range, 20.8–22.34 mm; n = 4). Mean intraocular pressures at the time of initial visit were 13.7 mmHg in the right eye and 12.9 mmHg in the left eye. Seven patients were able to complete color vision testing with either Ishihara color plates or the Farnsworth D-15 test; 2 patients showed normal color discrimination, and the remaining patients showed some level of color discrimination deficit, primarily along the tritan axis if tested with the Farnsworth D-15 test. Seven patients could participate in Goldmann visual field testing, and of these, 3 patients showed grossly full peripheral visual fields with a mildly enlarged blind spot (including the right eye of patient 9), 2 patients showed constriction with mid-peripheral ring scotomas, and 1 patient showed severely constricted fields. In 1 patient, Goldmann visual field testing was attempted, but the fixation target could not be visualized.

On anterior segment examination, no patients showed signs of anterior segment dysgenesis or signs of punctate epitheliopathy. Four patients underwent Schirmer tear testing, and tear production levels were within normal limits for all patients (with anesthesia: range, 15–20 mm in the right eye and 11–23 mm in the left eye). Three patients showed nongranulomatous keratic precipitates, 3 patients showed band keratopathy, including 2 patients with band keratopathy affecting the central visual axis, and 2 patients showed guttae. Seven eyes of 6 patients harbored cataracts, including nuclear (n = 3) and posterior subcapsular (n = 4); 1 eye with posterior subcapsular cataract also showed anterior capsular opacity. Three eyes from 2 patients were pseudophakic, and 2 eyes of 1 patient were aphakic; 10 eyes harbored clear lenses. Seven patients showed anterior uveitis in the form of trace to 1+ anterior chamber cell during at least 1 encounter, with 4 patients having a bilateral disease, and 14 eyes from 8 patients were observed to have trace to 2+ anterior vitreous cells.

All patients were able to complete dilated fundus examination. Before evaluation at the National Institutes of Health, 7 patients were noted to have a history of optic disc edema or optic disc elevation, and 6 patients reported a prior history of uveitis. Ten patients were observed to have optic disc elevation on our evaluation (Fig 1) (bilateral in 7 patients and no fundus view in 2 eyes of 2 patients), but none showed peripapillary exudates. One patient showed 1 splinter hemorrhage at the inferior disc margin in the right eye. Of these 10 patients, 6 patients demonstrated disc leakage on intravenous fluorescein angiography (IVFA; IVFA was not performed in 1 patient). A total of 6 patients were noted to have optic disc pallor, including 1 patient without optic disc elevation and 2 patients who harbored small superficial optic disc drusen visualized on examination and fundus autofluorescence imaging, not contributing to the significant disc elevation. All patients for whom we could obtain OCT imaging of the optic nerve showed severely elevated average retinal nerve fiber layer thicknesses bilaterally (right eye: mean, 235.7 μm; range, 136–427 μm; n = 9; left eye: mean, 218.3 μm; range, 131–356 μm; n = 7). Qualitatively, all patients demonstrated peripapillary thickening on OCT, and 6 patients showed peripapillary vascular changes including sclerotic vessels. Additionally, 7 patients demonstrated intraretinal hyperreflective peripapillary changes evident on OCT. Overall, the disc and peripapillary appearances were

symmetric between the 2 eyes. All of the patients in this cohort previously completed neuroimaging, without any mass lesion identified, and 9 of 11 patients underwent lumbar puncture (LP) with opening pressure noted to be within normal range.

Seven patients demonstrated fundus findings consistent with retinal degeneration: atrophy within the posterior pole with deeply pigmented confluent nummular deposits, rare bone spicule-like deposits, and vascular attenuation. In patients with earlier stage retinal disease, atrophy localized to the posterior pole and appeared to extend peripherally, as seen in those with more advanced disease (Fig 2). One patient was noted to show extensive fibrotic changes within the posterior pole. Notably, all patients showed appreciable vascular attenuation of far peripheral vessels, although less in those without degenerative changes. Seven patients were able to complete ffERG testing: 3 showed normal ffERG responses in 5 eyes (1 eye of patient 9 harbored a complete retinal detachment), 1 patient showed decreased photopic and scotopic responses consistent with CORD, whereas 3 patients with advanced disease showed signal that was indistinguishable from noise. Patient 3, who was found to have normal ffERG results, was able to complete visually evoked potential testing, which was also showed normal results; however, the electro-oculogram's Arden ratio was decreased at 1.25 in the right eye and 1.27 in the left eye (normal range, > 1.56). OCT findings of the macula in those with retinal degeneration were consistent with degenerative changes and showed diffuse ellipsoid zone loss in 13 eyes from 7 patients. Additionally, the retina was noted to have coarse lamination in the setting of significant outer retinal loss. One eye was noted to have a lamellar hole. The 3 patients without electrophysiologic evidence of CORD demonstrated normal-appearing macular OCT results.

Two patients demonstrated cystoid macular edema (CME). Patient 3 had CME refractory to topical prednisolone and ketorolac ophthalmic drops, as well as anakinra and adalimumab. The CME resolved only after oral prednisone treatment. In 9 eyes from 5 patients, IVFA showed retinal vascular changes consistent with retinal vasculitis. An additional 1 patient had demonstrated retinal vascular leakage on IVFA at an earlier visit with an outside physician. Furthermore, 11 eyes from 6 patients showed extensive window defects and staining, consistent with advanced degenerative changes. Three of the 11 patients were receiving systemic treatment at the baseline visit, including prednisone (n = 2; patients 9 and 11), canakinumab (n = 1; patient 6), and tocilizumab (n = 1; patient 9). The indication for treatment in 1 patient was intraocular inflammation. In the remaining 2 patients, it was the combination of both ocular and systemic findings. Notably, patient 9 was started on tocilizumab after treatment with multiple therapies, including anakinra, adalimumab, and methotrexate, failed. Additionally, 1 participant previously had received rituximab and intravenous immunoglobulin (IVIG), and another previously had been treated with prednisone.

Disease Course

Seven of the 11 patients were seen at follow-up encounters (mean duration of follow-up, 947 days; range, 119–1825 days). After the initial visit, the systemic immunomodulatory therapy for 4 patients either was changed or initiated, including adalimumab (n = 3), anakinra (n = 2), tocilizumab (n = 2), and methotrexate (n = 2). Furthermore, 1 patient

received dexamethasone implant injections between follow-up visits. Of these patients receiving treatment, most showed a stable disease course. Patient 3 showed improved retinal vascular leakage on fluorescein angiography and almost complete resolution of CME with corresponding improvement in visual acuity 1 month after a trial of oral prednisone (1 mg/kg); however, on tapering the prednisone, despite the trials of adalimumab, anakinra, and methotrexate, a reoccurrence of CME and an increase in retinal vascular leakage was noted. She subsequently achieved almost complete resolution of CME and improvement in retinal vascular leakage 2 months after the initiation of subcutaneous tocilizumab, and this improvement was maintained after 6 months of tocilizumab therapy (Fig 3). This participant's ffERG findings were relative stability over time, despite the difficulties with test participation because of age. Patient 11, who was receiving a chronic low dose of prednisone, showed an increase in retinal vascular leakage in the right eye but decreased leakage in the left eye. Finally, patient 9, who was receiving treatment with tocilizumab at the baseline visit at our institution, demonstrated improved retinal vascular leakage compared with results from fluorescein angiography performed at an outside facility.

Discussion

The ophthalmic manifestations of this newly described genetic disorder are complex, and the potential causes of vision loss are multifactorial. We propose that 3 main factors contribute to changes in visual function in these patients: optic nerve involvement, ocular inflammation including retinal vasculitis and cystoid macular edema, and retinal degeneration. The relative contribution of these factors and their association remain to be elucidated. Observations from our cohort suggest that in the early stages of ophthalmic disease, patients are able to maintain vision of 20/50 or better; as soon as the ophthalmic disease progresses, visual acuity drops to a level of legal blindness.

All patients showed optic disc changes, including a reported history of optic disc edema, optic disc elevation, or a pale disc evident on slit-lamp biomicroscopy. These findings were noted both in the setting of other ophthalmic features (retinal dystrophy and vasculitis) and on their own, suggesting that optic nerve and peripapillary elevation perhaps is the earliest and most common ophthalmic finding of ROSAH syndrome. The clinical appearances of the optic nerves in this cohort are atypical for classic inflammatory causes of disc edema and are disproportionate to the degree of inflammation observed. Furthermore, fluorescein angiography did not reveal typical optic disc leakage patterns. Because we observed this disc elevation in eyes without other signs of intraocular inflammation, we postulate the cause is not only secondary to intraocular inflammation but instead also may be related to the changes previously described on neuroimaging suggestive of primary central nervous system inflammation.

Additionally, optic disc elevation also may be related to the high relative expression of *ALPK1* in the optic disc.[2] Optic disc elevation is a reported feature of other hereditary disorders such as Leber hereditary optic neuropathy and lysosomal storage disorders. Smith et al[9] described swelling of the nerve fiber layer in the setting of absent leakage on fluorescein angiography during the acute phase of Leber hereditary optic neuropathy. Subsequent authors have hypothesized that this represents axoplasmic flow stasis resulting

from retinal ganglion cell injury and that as the disease progresses, the mild disc elevation develops into optic disc pallor and atrophy. The disc edema noted in mucopolysaccharidosis types I and IV is thought to be related to glycosaminoglycan deposition, concomitant increased intracranial pressure, or both, which, if left untreated, also progresses to atrophy.[10,11] Although the cause of disc elevation in this cohort remains unclear, we postulate that several factors may be implicated, including intraocular inflammation, central nervous system inflammation, and structural changes resulting from relative high optic disc expression of *ALPK1*. Notably, optic disc pallor also was observed in 6 patients. Given that the disc pallor (with the exception of 1 patient) was see in patient with advanced degenerative changes, it remains unclear to what degree this is a consequence of the optic disc elevation, inflammation, retinal degeneration, or a combination thereof. Given that headache is a well-described systemic feature of ROSAH syndrome, increased intracranial pressure has been investigated as the cause of optic nerve elevation in these patients; however, previous groups reported normal intracranial pressure as measured by lumbar puncture (LP).[2,3] All of the patients in the present cohort previously completed neuroimaging, and those who underwent LP were found to have normal opening pressure, providing further evidence that increased intracranial pressure is not a contributory factor to the disc findings in this syndrome. Additionally, no significant hemorrhages or exudates were noted in any of these patients despite the level of disc elevation. Notably, of those patients who had magnetic resonance imaging of the orbit available, optic nerve enhancement was absent. As we continue to expand our understanding of ROSAH syndrome, the authors recommend consideration of initial evaluation for papilledema in any patient with unknown cause of disc elevation, with magnetic resonance imaging, magnetic resonance venography (MRV), and LP with opening pressure to rule out any treatable diagnoses; however, repeat LPs may be unnecessary unless the patient notes changes or is newly symptomatic.

Of note, patients with limited growth and development of the globe can demonstrate crowded or full appearing nerves. The mean axial length in this cohort was 21.7 mm, which is subnormal for patients older than 4 years, and 2 patients had a history of primary angle closure, likely contributing to catastrophic vision loss. These patients should be counseled and monitored closely for angle-closure glaucoma and consideration for prophylactic laser iridotomy as we learn more about the role of *ALPK1* in ocular development. Notably, only 2 patients had optic disc drusen, but both were small and anterior, not contributing to disc elevation.

Activation of *ALPK1* results in activation of the NF-κB pathway, a critical mediator of proinflammatory responses.[5] Dysregulation of the NF-κB pathway has been implicated in the pathogenesis of other autoinflammatory syndromes, such as Behçet's disease, Blau syndrome, and haploinsufficiency of A20, all of which are associated with uveitis.[12–14] Of note, we observed only low-grade cellularity in this cohort, which was consistent with prior reports and in contrast to the spectrum of the aforementioned diseases. Diffuse small-vessel retinal vasculitis was observed in 5 patients, with an additional patient showing leakage on IVFA carried out at an outside facility, although these changes typically were in patients with less advanced retinal degenerative changes.

To date, no consensus exists on the treatment for ROSAH syndrome. In a recent report by Kozycki et al,[6] 7 of 10 patients treated with biologics noted subjective improvement in systemic symptoms. Additionally, 3 of 4 patients receiving adalimumab showed normalization of C-reactive protein levels. A report by Zhong et al[1] observed an improvement of uveitis on adalimumab therapy; however, persistent optic disc edema and progressive visual deterioration were noted. Other work has described the uveitis in ROSAH syndrome as unresponsive to immunomodulatory therapies.[2] In the present cohort, patient 3 demonstrated a therapeutic response of intraocular inflammation to oral prednisone but demonstrated CME and retinal vasculitis refractory to the combination of adalimumab, anakinra, and methotrexate. The patient subsequently responded to changing anakinra to tocilizumab. Patient 9 also showed improved retinal vascular leakage after treatment with tocilizumab. Notably, tocilizumab has demonstrated efficacy in uveitic cystoid macular edema compared with tumor necrosis factor α inhibitors.[15] However, most patients in this cohort showed advanced disease, making it challenging to assess the efficacy and thus potential benefit of immunomodulatory therapy. Further characterization of this disorder is necessary to identify potential therapeutic targets.

ALPK1 has been shown to be expressed in both the retina and retinal pigment epithelium (RPE), and localization of *ALPK1* to photoreceptor basal bodies of connecting cilia was established by Williams et al.[2] Consequently, dysfunctional cilia function, ciliary-centrosomal abnormality, disrupted cell cycle regulation, as well as abnormal RPE polarity all have been proposed as the underlying cause of the retinal degeneration features of ROSAH syndrome; however, it is unclear to what extent the photoreceptors and RPE contribute to disease phenotype.[2] One patient in our cohort with normal ffERG findings demonstrated an abnormal Arden ratio on electro-oculography, suggesting for the first time on a clinical basis that RPE dysfunction may occur before photoreceptor dysfunction and classic findings of retinal dystrophy are noted on examination. Additional psychophysical testing early in the disease course may help to elucidate the primary cause of retinal dystrophy in these patients.

Most patients in this cohort demonstrated a phenotype on the CORD spectrum, with atrophic changes localizing to the posterior pole in early disease, later extending to the periphery, consistent with what is seen typically in other patients with CORD. However, patients with ROSAH syndrome demonstrate an atypical pigment pattern, specifically deeply pigmented nummular deposits, previously described in *CRB1*-related retinal dystrophy,[16,17] and enhanced S-cone syndrome.[18,19] As in these other conditions, nummular pigment was noted most often in patients with RPE atrophy and more advanced stages of disease. Curiously, also as previously described in *CRB1*-related retinal dystrophy,[16,17] patients with ROSAH syndrome with retinal degeneration showed disorganized lamination of the retina on OCT in the presence or absence of significant thinning. A retinal dystrophy with nummular pigment deposits primarily affecting the posterior pole associated with optic disc elevation should raise suspicion for ROSAH syndrome. Previous reports have implicated inflammatory mediators in other inherited retinal degeneration,[20–24] and this has been considered in patients with ROSAH syndrome; however, 3 patients in this cohort sought treatment without any signs of retinal dystrophy while demonstrating vascular leakage and cellularity. Thus, it remains to be determined whether the retinal dystrophy in ROSAH

syndrome represents an independent process, rather than the result of chronic untreated inflammation. Additionally, the CME observed in patient 1 likely represents a degenerative process.

In summary, ROSAH syndrome is a rare, autosomal dominant cause of retinal dystrophy, optic disc elevation, and intraocular inflammation. We report for the first time systematic deep characterization of the 3 main factors contributing to vision loss in a large cohort of patients with ROSAH syndrome. Retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and headache syndrome should be considered in the differential diagnosis of patients with retinal dystrophy with nummular pigmentary changes in combination with the other aforementioned features. Longitudinal follow-up suggests a progressive course. Treatment of uveitis in earlier presentations with tocilizumab could be considered; however, further work is necessary in an expanded cohort of patients to replicate these observations. Furthermore, the retinal degeneration and optic disc changes may be independent of the intraocular inflammation observed. Awareness of this rare syndrome is key to diagnosis because patients may seek treatment from an ophthalmologist first with visual symptoms, and commercially available retinal dystrophy panels typically do not include *ALPK1*. This report of deep phenotyping of a large cohort of patients with ROSAH syndrome expands recognition and understanding of the ocular manifestations of this *ALPK1*-related autoinflammatory disease and guides management and calls for an inclusion of the *ALPK1* in molecular genetic diagnostic panels specific for inherited retinal diseases.

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Abbreviations and Acronyms:

ALPK1	alpha kinase 1
CME	cystoid macular edema
CORD	cone–rod dystrophy
D	diopter
ffERG	full-field electroretinography
IVFA	intravenous fluorescein angiography
LP	lumbar puncture
NF-κB	nuclear factor kappa B
ROSAH	retinal dystrophy
optic nerve edema	splenomegaly
anhidrosis	and headache

RPE	retinal pigment epithelium

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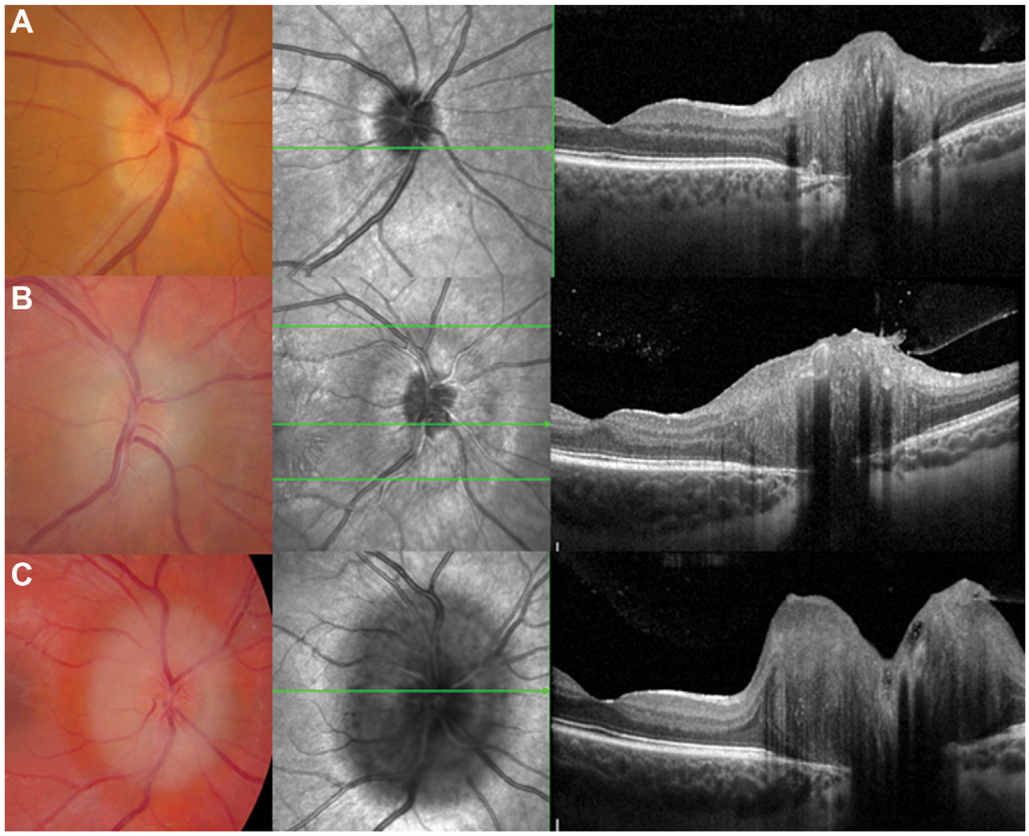

Figure 1.

Optic disc elevation in retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and headache syndrome. **Left column,** Color fundus photographs showing disc elevation with only mild disc margin blurring in (**A**) (patient 8) and much more pronounced disc elevation and margin blurring in (**B**) (patient 9) and (**C**) (patient 3). **Middle and right columns,** with infrared image of the optic nerve and corresponding OCT imaging.

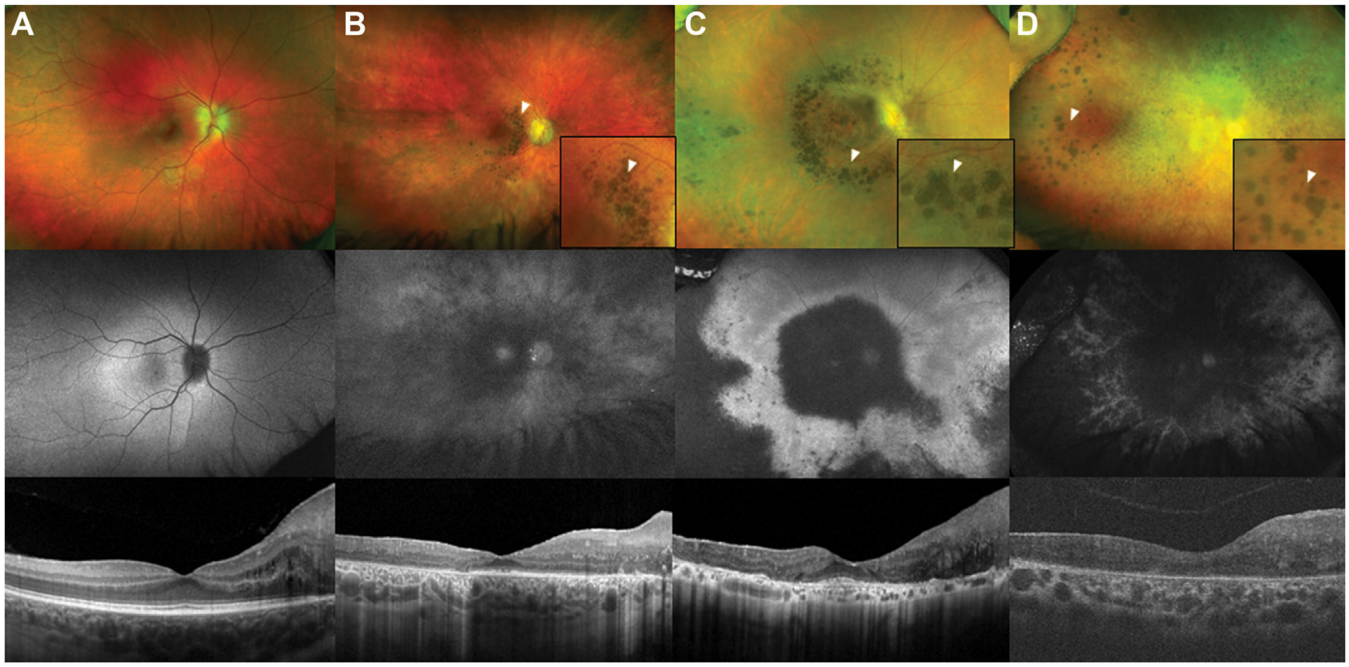

Figure 2.

Retinal findings on (**Top row**) ultra-widefield color images, (Middle row) fundus autofluorescence (FAF) images, and (**bottom row**) macular OCT images. Patients with early disease show disc elevation and normal-appearing retina on color imaging, FAF imaging, and OCT (**A**) (patient 3), whereas those with more advanced disease (**B–D**) (patients 7, 11, and 5, respectively) demonstrate a range of posterior pole nummular pigment (white arrowhead, magnified inset), vascular attenuation, and retinal pigment epithelium and photoreceptor atrophy. In patients with more advanced retinal degeneration, coarse lamination of the retinal layers are noted on OCT (**C, D**).

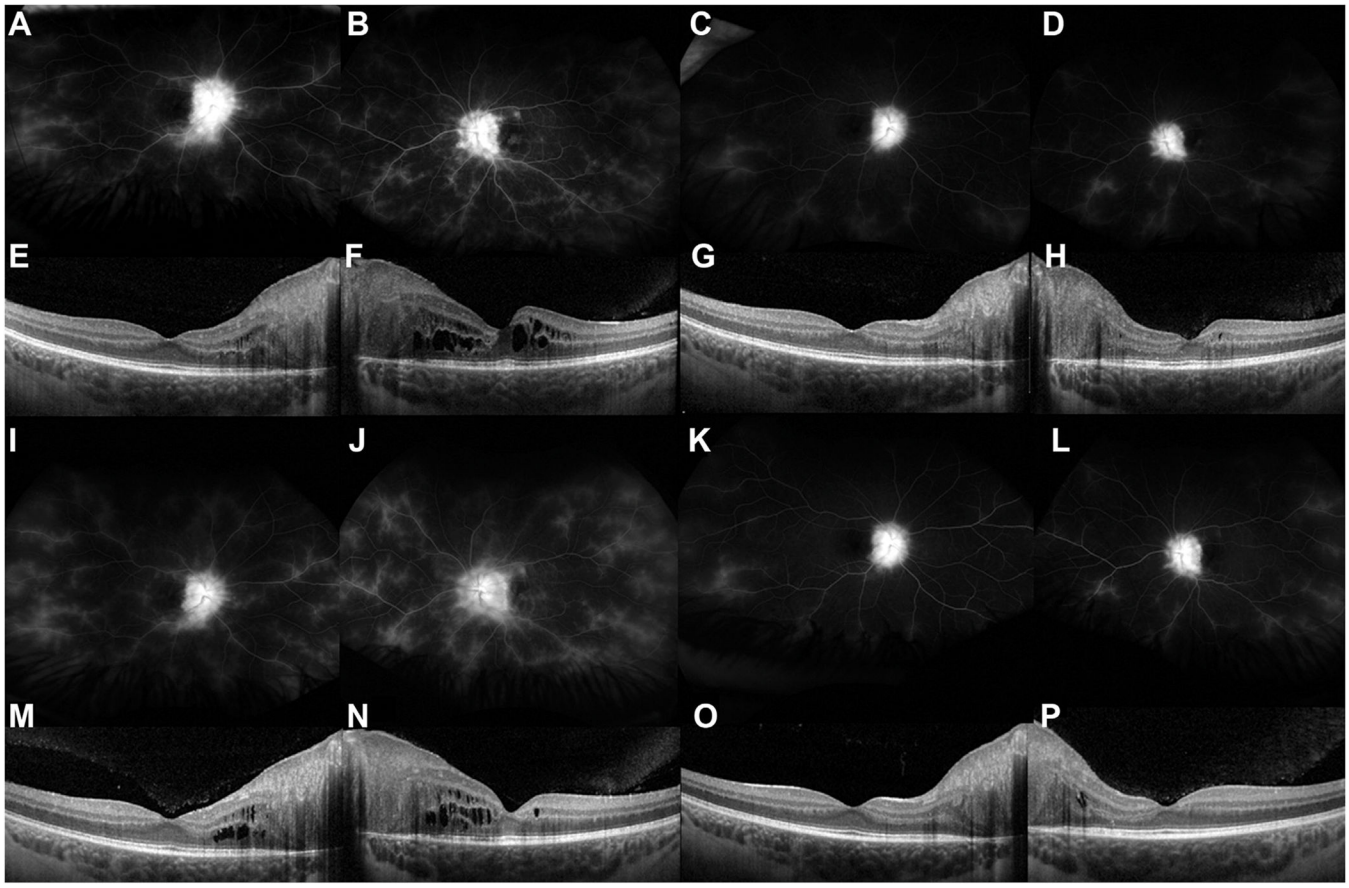

Figure 3.

Longitudinal ultra-widefield fluorescein angiography and OCT images of patient 3 showing changes in response to treatment. Fluorescein angiography and OCT images of the right eye (**A, E**) and left eye (**B, F**) obtained while the patient was receiving treatment with adalimumab weekly. Fluorescein angiography (**A, B**) revealed disc and peripapillary leakage as well as diffuse small-vessel leakage in both eyes, and cystoid macular edema (CME) was observed bilaterally (**E, F**). Improved disc retinal vascular leakage (**C, D**) and CME (**G, H**) was noted in both eyes after initiation of oral prednisone (1 mg/kg) in addition to methotrexate and adalimumab weekly. A recurrence of both retinal vascular leakage (**I, J**) and CME (**M, N**) was observed on tapering prednisone, while continuing anakinra 400 mg daily, adalimumab weekly, and methotrexate. A notable improvement in retinal vascular leakage (**K, L**) and almost complete resolution of CME (**O, P**) was noted after replacing anakinra with tocilizumab every 2 weeks subcutaneously.

Table 1.

Patient Summary

Patient No.	*ALPK1* Variant	Age at Visit (yrs)	Sex	Visual Acuity		Retinopathy						Optic Nerve Elevation	Splenomegaly	Anhydrosis or Hypohidrosis	Headache
						Retinal Degeneration		*Uveitis or Vasculitis*							
				Right Eye	*Left Eye*	*Yes or No*	*Full-field Electroretinography Findings*	*Anterior Chamber Cell*	*Vitreous Cell*	*Cystoid Macular Edema*	*Vasculitis*				
1	c.710C→T p.(Thr237Met)	58.9	F	20/250	NLP	Yes	—	0	Trace/—	Yes	—	Yes	Unknown (no prior imaging)	Yes	Yes
2	c.710C→T p.(Thr237Met)	32.1	F	20/800	20/800	Yes	No signal above noise at ERG performed 2 yrs after baseline visit	Trace/0	1	No	No	Yes	Yes	Yes	Yes
3	c.710C→T p.(Thr237Met)	11.0	F	20/20	20/40	No	Normal in both eyes	0/Trace	1	Yes	Yes	Yes	Yes	Yes	Yes
4	c.710C→T p.(Thr237Met)	7.3	F	LP*	LP*	—	—	0	0	—	—	No	Yes	Yes	Unknown (nonverbal with cerebral palsy)
5	c.710C→T p.(Thr237Met)	23.3	F	LP	20/250	Yes	No signal above noise	0	1	No	—	Yes	No	Yes	Yes
6	c.710C→T p.(Thr237Met)	25.7	M	20/500	20/200	Yes	—	0	0/Trace	No	Yes	Yes	Yes	Yes	Yes
7	c.710C→T p.(Thr237Met)	17.9	M	20/160	20/160	Yes	No signal above noise	Trace	3	No	Yes	Yes	Yes	Yes	No
8	c.710C→T p.(Thr237Met)	42.4	M	20/16	20/16	No	Normal in both eyes	Trace/1	0	No	Yes	Yes	Yes	Yes	Yes
9	c.710C→T p.(Thr237Met)	14.3	M	20/16	LP	No	Normal in right eye; no signal above noise in left eye (retinal detachment)	0/Trace	Trace/1	No	No	Yes	Yes	Yes	Yes
10	c.710C→T p.(Thr237Met)	60.2	M	NLP	NLP	Yes	—	0	0	No	No	Yes	Yes	Yes	No

Patient No.	*ALPK1* Variant	Age at Visit (yrs)	Sex	Visual Acuity		Retinopathy						Optic Nerve Elevation	Splenomegaly	Anhydrosis or Hypohidrosis	Headache
						Retinal Degeneration		*Uveitis or Vasculitis*							
				Right Eye	*Left Eye*	*Yes or No*	*Full-field Electroretinography Findings*	*Anterior Chamber Cell*	*Vitreous Cell*	*Cystoid Macular Edema*	*Vasculitis*				
11	c.761A/G p. (Tyr254Cys)	37.6	F	20/40	20/80	Yes	Cone–rod dystrophy	1	0	No	Yes	Yes	Yes	Yes	No

ERG = electroretinography; F = female; LP = light perception; M = male; NLP = no light perception; — = not available.

Patients 1—4 represent 3 generations of 1 family, and patients 8 and 9 represent 2 generations of another family; the remaining patients are unrelated.

* Visual acuity testing limited by ability to cooperate with testing.