ROSAH syndrome mimicking chronic uveitis

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Clin Genet. 2023 Apr;103(4):453-458.
doi: 10.1111/cge.14286. Epub 2022 Dec 30.

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Short Report

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Running Title

ROSAH syndrome mimicking uveitis

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FUNDING/SUPPORT/SPONSORS

None

CONFLICT OF INTEREST:

None

CONSENT FROM PATIENTS:

Obtained.

ACKNOWLEDGEMENT

None

PRIOR PRESENTATION

None

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Abstract

Purpose: To suggest a unique missense variant candidate based on long term ophthalmological changes and associated systemic signs described in unrelated families affected by an autosomal dominant multi-systemic disorder including Retinal dystrophy, Optic nerve edema, Splenomegaly, Anhidrosis and migraine Headaches, called ROSAH syndrome, related to a unique missense variant in *ALPK1* gene. **Design**: Observational longitudinal followup study of unrelated families... **Methods:** Clinical analysis of ophthalmological and systemic examinations was performed followed by genetic analysis including targeted Next Generation Sequencing (NGS), and Whole-Genome Sequencing (WGS). **Results:** The ophthalmological phenotype showed extensive optic nerve swelling - associated with early macular oedema and vascular leakage. Main associated systemic manifestations were recurrent fever, splenomegaly, anhidrosis, mild cytopenia, anicocytosis and hypersegmented polynuclear cells. WGS, shortened in the second family by the gene candidate suggestion, revealed in all patients the heterozygous missense variant c.710C>T; p.(Thr237Met) in *ALPK1*. **Conclusions:** The main morbidity in ROSAH syndrome appeared ophthalmological. Comprehensive retinal phenotype changes and detailed systemic and family history aided by the advancement in genetic testing may allow an early diagnosis of ROSAH syndrome. Multidisplinary team discussion could help in the adaptation of systemic immunosuppressive treatment levels. The unique missense variant may be further suggested as a target of gene correction therapy.

Introduction Retinal dystrophies (RD) are a group of inherited degenerative disorders characterized by a progressive damage of photoreceptor cells and retinal pigmentary epithelium (RPE).[1] Despite the good performances of Next Generation Sequencing (NGS) of

targeted RD genes (PMID 30718709), the use of Whole-Exome Sequencing (WES) and Whole-Genome Sequencing (WGS) combined with clinical analysis has improved the diagnosis of rare syndromic retinal dystrophies. WGS lead to the recent identification of *ALPK1* gene as the cause of the ocular systemic disorder called ROSAH syndrome, due to its clinical features including familial autosomal dominant Retinal dystrophy, Optic nerve edema, Splenomegaly, Anhidrosis and migraine Headaches syndrome.[2,3]

We report the ophthalmological changes, systemic features and genetic analysis in patients from 2 unrelated families treated as bilateral chronic posterior uveitis. [2,5]

Material and Methods

This longitudinal observational follow-up study included 5 patients from 2 unrelated families.

A full clinical and ophthalmological workup including autoimmune, infectious, storage disease and genetic studies, has been performed. Detailed ophthalmological tests are displayed in supplementary documents.

Ethics and consents

The current study was approved on November 10th of 2021 by an institutional review board in Montpellier University Hospital (IRB ID:202100959) . The study was conducted in compliance with good clinical practice and followed the tenets of the Declaration of Helsinki. Informed written consents were obtained in accordance with the French bio-ethics law n°2011-814, decree 2013-527, from patients and from the parents of minors. Written photo consent has been obtained from each involved patient.

Molecular Analysis

Genetic analysis used different NGS panels including main genes known to be associated with autosomal dominant inherited Retinal dystrophies and were unsuccessfull to identify the causal pathogenic variant. With recent knowledge of novel syndromes from Chronic infantile neurological cutaneous articular (CINCA) to ROSAH syndromes, - WGS were required to identify the pathogenic variant previously reported in Rosah syndrome. Sanger sequencing was used to confirm the results obtained from WGS. High-quality genomic DNA samples were randomly fragmented by Covaris Technology. Detailed methods are shown in supplementary document.

Results

Main clinical and biological features at admission are summarized in the table.

First family:

Patient 1, the proband:

A 11-year-old boy presented with bilateral decrease in his visual acuity (VA) to 20/200 in the right eye (RE) and 20/80 in left eye (LE). Anterior segment examination was not remarkable. Vitreous examination showed vitreous cells graded as 1+ in both eyes. Fundus examination showed an optic nerve head swelling and macular edema in both eyes (fig 1).

Cerebral Magnetic Resonance Imaging (MRI) showed normal ventricles and optic pathways. Lumbar puncture was performed to rule out intracranial pressure and was normal. Magnetic resonance spectroscopy showed a very high choline peak suggesting degradation of myelin. There were no anomalies in 4-axis arteriography. The patient has undergone a lumbo-peritoneal shunt at the age of 10 years for chronic bilateral papilledema along with campimetric worsening abnormalities.

Ten years later **,** VA was 20/2000 RE and 20/125 LE. The patient complained of photophobia mandated the use of external tinted glasses. Fundus examination revealed intra retinal peripapillary exudates in the RE and superficial flame shaped haemorrhage in the LE on the optic nerve head swelling, with appearance of pigmented changes in clumps predominant in the periphery of the macular area.

Associated main systemic signs were recurrent fever at 39.5 C degrees every 6-8 weeks, splenomegaly, eczema, anhidrosis, thin hair. At the age of 18 years, he developed severe *Epstein Barr Virus* (EBV) infection.

Patient 2, the proband's brother. The youngest brother was admitted on the same day at the age of 6 years. At admission, VA was 20/20 in both eyes. Fundus exam showed vitreous 0.5+ cells, bilateral papillary edema in both eyes with fine flame shaped haemorrhages on the margins of papillary swelling. Brain MRI and lumbar pressure were normal. Main associated signs were recurrent fever spikes, headaches, lower back pain, splenomegaly, anhidrosis, nail dystrophy, thin hair, and dental problems. Ten years later, VA was 20/200 RE and 20/125 LE. Fundus showed optic nerve swelling and OCT showed macular cysts

Patient 3, father's proband, 50 years old, presented decreased in visual acuity since the age of seven years and chronic bilateral papilledema. He was admitted the same day at the age of 50 years with legal blindness. He had chiasmata decompression at the age of 10 years. Main associated signs were diarrhoea, weekly fever, and splenomegaly.

Wide workup results:

Immune workup showed in the 3 patients, a platelet count at about 140,000/mm3 and poikilocytosis. The C-reactive protein (CRP) was normal outside of feverish periods. Infectious serologies were negative. Lysosomal diseases were ruled out, in particular Gaucher

disease and Niemann-Pick. The leukocyte activity of acid sphingomyelinase was normal. Search of lymphadenopathy, infectious, autoimmune or tumour causes was negative.

Treatment

Treatment was started by acetazolamide (250mg 3 times a day) followed by systemic prednisone, successively associated with methotrexate, azathioprine, colchicine.anakinra, adalimumaband infliximab. Anakinra worsened the opthalmological picture, infliximab was effective on recurrent fever while no effect on VA and retinal features.

Genetic analysis carried out in 2003, 2007 and 2011 identified no variant in genes associated with retinitis pigmentosa and cone-rod dystrophy, and no causal variant in genes involved in hereditary fevers, particularly TNF receptor associated periodic syndrome (*TNFRSF1A*) and Familial Mediterranean fever (*MEFV)* , as well as *NLRP3* responsible for *CINCA* syndrome and mevalonate kinase deficiency (*MVK*).

A variant of unknown significance was identified in exon 4 of *NOD2*, but was further excluded as it did not segregate with the disease.

The heterozygous missense variant c.710C>T, p.(Thr237Met) located in exon 9 of *ALPK1* (NM_025144.4) was identified by WGS in both children of the first family and in the other unrelated boy and his father. The c.710C>T variant is rare because not present in gnomAD database. It is highly conserved and physicochemical distance between threonine and methionine is high (Grantham distance of 81) with a CADD score of 22.9. This variation is considered as likely pathogenic (SNV4) according to the ACMG (*American College of Medical Genetics and Genomics*) 2015 classification criteria [4] and was previously reported to cause ROSAH syndrome. [2,5]

Patient 4 ,**unrelated 14 years old boy,** complaining of visual loss in the left eye since early childhood, initially related to a bilateral non-granulomatous posterior uveitis showing bilateral diffuse papillary edema and posterior pole inferior exudation in the left eye. Associated systemic signs were splenomegaly, homogeneous hepatomegaly and polar kidney cyst. Familial history included: (1) father with no visual complains but exhibiting bilateral papillary edema in fundus exam, associated to recurrent unexplained fever and splenomegaly for which a splenectomy was performed, (2) great paternal father had uveitis associated with hepatosplenomegaly and polycystic kidney lesions.

A wide immune and infectious work-up was negative. The brain MRI showed stable hypersignal in white matter located in parahyppocampus gyrus with no contrast enhancing. No change was noticed in the further years. Medullar MRI was normal. Spinal fluid was normal

Treatments included prednisone successively associated with anakinra, adalimumab, methotrexate, and tocilizumab. No ophthalmological significant response was seen.

The genetic investigations ruled out an enzyme deficiency disease*: (mevalonic aciduria negative, no deficiency in CD70, CGH array negative).* The combination of ophthalmological, systemic signs and familial history, allowed to suggest ROSAH syndrome and *ALPK1* as a candidate gene. So in the next weeks the heterozygous missense variant c.710C>T, p.(Thr237Met) located in exon 9 of *ALPK1* was identified by NGS genes panel in both child and father.

Discussion

The current study confirms the association of a unique variant missense in ALPK1 as a guide diagnosis of ROSAH using the WGS.

Different genomic technologies lead to the diagnosis of ROSAH syndrome in identifying the causing variant in *ALPK1* in five unrelated families.[2,3] Episodic fever was a prominent feature in our patients and in two previously described patients with ROSAH syndrome, as well as mild pancytopenia[2]. The patients reported in this study presented similar ophthalmological features as the ones previously described although small sample size.[2] The earliest feature is decreased vision associated with optic nerve head edema seen on ophthalmic examination. Intracranial pressure was within normal limits in all patients. [2,3]

ALPK1 is an alpha-protein kinase belonging to a class of atypical protein kinases, which could have critical role in centrosome and cilia biology. Given the centrosomal, spindle poles and primary cilia localization of *ALPK1*, Williams et al. hypothesized that abnormal cilia function may be due to *ALPK1* pathogenic variant, p.(Thr237Met).[6] On the other hand, *ALPK1* has been involved in mediates innate immune responses toward bacterial infections, through regulation of NF-κB signalling. [6] More studies are needed to suggest ROSAH syndrome taking part in a precise systemic diseases group.

Several clinical elements were considered as underplayed by auto-immune mechanism, such as chronic macular edema (CME), fluorescein leakage in retinal angiography, and cells in vitreous noted at 1+ on Sun scale. However, these three elements are compatible with diagnosis of retinal dystrophy.

Interestingly, inflammatory mechanisms have been shown in typical RP. In particular, numerous inflammatory components have been found in the aqueous humor and vitreous fluid of typical RP eyes. They could participate in photoreceptor apoptosis via the activation of the retinal micro and macroglia. [7] However, in the previously reported patients, and in the four

234 treated current patients, long term immunosuppressive treatment did not prevent retinal
235 damages.
236
237 **Conclusion**

238 Comprehensive detailed phenotype changes aided by the advancement in genetic testing could
239 allow an early genetic diagnosis of ROSAH syndrome. Multidisplinary team discussion helps
240 in the adaptation of systemic immunosuppressive treatment levels. The unique missense
241 variant may be suggested as a target of gene correction therapy.

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Figure legends Fig 1- Proband's brother in the family 1 . At 16 year-old boy showed a BCVA at 20/200 in RE and 20/125 in LE.

A. RE B. LE retinography showing papillary edema, prepapillary sheathed arteries, centromacular atrophy following chronic intraretinal cysts.

C. RE D. LE Posterior pole autofluorescence showing large macular hypoautofluorescence area surrounded by hyperautofluorescent ring.

E. RE F LE horizontal central OCT scan showing foveal atrophy associated with few intra nuclear layer cysts, and thickened peripapillary area

Fig 2 Proband in the family 2 .A 14 year-old boy showed a BCVA at 20/20 in RE and light perception in LE. A.RE retinography showed papillar edema B. LE retinography showed exudative chronic papillomacular detachment and peripapillary intra retinal hemorrhages.

C. D Posterior pole autofluorescence showed hyperfluorescent ring in the RE and large hyperfluorescent area corresponding to exudative detachment.

Table title : Main clinical and biological signs at admission of patients diagnosed with ROSAH syndrome

	Ophthalmological signs						Systemic signs				Biological results			
Patient Gender age	Family history Papillary edema Uveitis	BCVA* RE LE	Fundus	Posterior pole Auto Fluorescence	Macular OCT	Visual field	Recurrent fever	Spleno megaly	Severe EBV infection history	Anhidrosis	Blood count	Blood smear	Anti nuclear antibodies	Others auto anti bodies
Family 1 Proband M 11 yo	present	20/200 20/80	Extensive papillary edema	Hyperauto Fluorescent ring surrounding a large hypoauto fluorescent macular area	Macular edema changing towards atrophy	Coeco central scotoma	Present	present	present	present	Low platelet count 100000/mm3	poikilocytosis hyper segmented polynuclear cells	Present 1/2560 DFS [1] 70 aspect	negative
Family 1 Proband ' Brother M 6 yo	present	20/20 20/20	Extensive papillary edema	Hyperauto Fluorescent ring surrounding a large hypoauto fluorescent macular area	Macular edema changing towards atrophy	Enlarged Mariotte spot changing towards coeco central scotoma	present	present	absent	present	Low platelet count 100000/mm3	NA[2]	Present 1/160	negative
Family 1 Proband' Father M 50 yo	present	1/200 1/100	Extensive papillaryedema	large hypoauto fluorescent macular area	Macular edema changing towards atrophy	NA	present	present	ND[3]	present	platelets 100.000-150,000/ mm3 Leukopenia	anisocytosis anisochromia, poikilocytosis hyper segmented polynuclear cells	ND	negative
Family 2 Proband M 14 yo	present	20/20 1/200	Extensive papillary edema	Hyperauto Fluorescent ring surrounding papillar edema	Macular edema in LE	Enlarged Mariotte spot in RE NA in LE	present	present	absent	present	Low count in normal range	poikylocytosis	1/160	negative
Family 2 Proband' Father M 43 yo	present	20/20 20/20	Extensive papillary edema	Hyperauto Fluorescent ring surrounding papillar edema	normal	Enlarged Mariotte spot	present	Present splenectomy	present	present	normal	Howell-Jolly corpus	negative	negative

Foot notes:

BCVA: Best corrected visual aquityDFS: Dense fine speckled

NA: Not applicable

ND: not detected