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ROSAH syndrome mimicking chronic uveitis

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3 ROSAH syndrome mimicking 4 chronic uveitis

5 Short Report

6 Title **ROSAH syndrome mimicking chronic uveitis**

7

8 **Running Title**

9 ROSAH syndrome mimicking uveitis

10

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72 **Abstract**

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

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

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

101 We report the ophthalmological changes, systemic features and genetic analysis in patients
102 from 2 unrelated families treated as bilateral chronic posterior uveitis.^{2,5}

103 **Material and Methods**

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

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

108 Ethics and consents

109 The current study was approved on November 10th of 2021 by an institutional review board in
110 Montpellier University Hospital (IRB ID:202100959) . The study was conducted in compliance
111 with good clinical practice and followed the tenets of the Declaration of Helsinki. Informed written
112 consents were obtained in accordance with the French bio-ethics law n°2011-814, decree
113 2013-527, from patients and from the parents of minors. Written photo consent has been
114 obtained from each involved patient.

115

116 Molecular Analysis

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

125

126 **Results**

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

128 **First family:**

129 **Patient 1, the proband:**

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

134 Cerebral Magnetic Resonance Imaging (MRI) showed normal ventricles and optic pathways.

135 Lumbar puncture was performed to rule out intracranial pressure and was normal. Magnetic
136 resonance spectroscopy showed a very high choline peak suggesting degradation of myelin.

137 There were no anomalies in 4-axis arteriography. The patient has undergone a lumbo-
138 peritoneal shunt at the age of 10 years for chronic bilateral papilledema along with
139 campimetric worsening abnormalities.

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

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

148

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

156 **Patient 3, father's proband, 50 years old,** presented decreased in visual acuity since the age
157 of seven years and chronic bilateral papilledema. He was admitted the same day at the age of
158 50 years with legal blindness. He had chiasmata decompression at the age of 10 years. Main
159 associated signs were diarrhoea, weekly fever, and splenomegaly.

160 Wide workup results:

161 Immune workup showed in the 3 patients, a platelet count at about 140,000/mm³ and
162 poikilocytosis. The C-reactive protein (CRP) was normal outside of feverish periods.

163 Infectious serologies were negative. Lysosomal diseases were ruled out, in particular Gaucher

164 disease and Niemann-Pick. The leukocyte activity of acid sphingomyelinase was normal.

165 Search of lymphadenopathy, infectious, autoimmune or tumour causes was negative.

166 Treatment

167 Treatment was started by acetazolamide (250mg 3 times a day) followed by systemic

168 prednisone, successively associated with methotrexate, azathioprine, colchicine, anakinra,

169 adalimumab and infliximab. Anakinra worsened the ophthalmological picture, infliximab was

170 effective on recurrent fever while no effect on VA and retinal features.

171 **Genetic analysis** carried out in 2003, 2007 and 2011 identified no variant in genes associated

172 with retinitis pigmentosa and cone-rod dystrophy, and no causal variant in genes involved in

173 hereditary fevers, particularly TNF receptor associated periodic syndrome (*TNFRSF1A*) and

174 Familial Mediterranean fever (*MEFV*), as well as *NLRP3* responsible for *CINCA* syndrome

175 and mevalonate kinase deficiency (*MVK*).

176 A variant of unknown significance was identified in exon 4 of *NOD2*, but was further

177 excluded as it did not segregate with the disease.

178 The heterozygous missense variant c.710C>T, p.(Thr237Met) located in exon 9 of *ALPK1*

179 (NM_025144.4) was identified by WGS in both children of the first family and in the other

180 unrelated boy and his father. The c.710C>T variant is rare because not present in gnomAD

181 database. It is highly conserved and physicochemical distance between threonine and

182 methionine is high (Grantham distance of 81) with a CADD score of 22.9. This variation is

183 considered as likely pathogenic (SNV4) according to the ACMG (*American College of*

184 *Medical Genetics and Genomics*) 2015 classification criteria⁴ and was previously reported to

185 cause ROSAH syndrome.^{2,5}

186

187

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

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

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

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

208

209 **Discussion**

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

212 Different genomic technologies lead to the diagnosis of ROSAH syndrome in identifying the
213 causing variant in *ALPK1* in five unrelated families.^{2,3} Episodic fever was a prominent feature
214 in our patients and in two previously described patients with ROSAH syndrome, as well as
215 mild pancytopenia². The patients reported in this study presented similar ophthalmological
216 features as the ones previously described although small sample size.² The earliest feature is
217 decreased vision associated with optic nerve head edema seen on ophthalmic examination.
218 Intracranial pressure was within normal limits in all patients. ^{2,3}

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

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

230 Interestingly, inflammatory mechanisms have been shown in typical RP. In particular,
231 numerous inflammatory components have been found in the aqueous humor and vitreous fluid
232 of typical RP eyes. They could participate in photoreceptor apoptosis via the activation of the
233 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. Multidisciplinary 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	Family	BCVA	Fundus	Posterior pole Auto	Macular	Visual field	Recurrent fever	Spleno	Severe	Anhidrosis	Blood	Blood	Anti	Others
Gender	history	RE		Fluorescence	OCT			megaly	EBV		count	smear	nuclear antibodies	auto
age	Papillary edema	LE							infection					anti
	Uveitis								history					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 '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 papillary edema	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	poikilocytosis	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 aquity DFS: Dense fine speckled

NA: Not applicable

ND: not detected

