The eye involvement in monogenic autoinflammatory diseases: literature review and update

J. Sota[1], A. Vitale[1], C. Fabiani[2], B. Frediani[1], D. Rigante[3], G.M. Tosi[4], M.E. Zannin[5], L. Cantarini[1]

[1]*Research Centre of Systemic Autoinflammatory Diseases, Behçet's Disease and Rheumatology-Ophthalmology Collaborative Uveitis Centre, Department of Medical Sciences, Surgery and Neuro-Sciences, University of Siena;*
[2]*Department of Ophthalmology, Humanitas Clinical and Research Centre, Rozzano (Milan);*
[3]*Institute of Paediatrics, Università Cattolica Sacro Cuore, Fondazione Policlinico Universitario "A. Gemelli", Rome;*
[4]*Ophthalmology Unit of the Department of Medicine, Surgery and Neuroscience, University of Siena;*
[5]*Department of Paediatrics, University of Padova, Italy.*

Jurgen Sota, MD*
Antonio Vitale, MD*
Claudia Fabiani, MD
Bruno Frediani, MD
Donato Rigante, MD
Gian Marco Tosi, MD
Maria E. Zannin, MD
Luca Cantarini, MD, PhD

**J. Sota and A. Vitale have contributed equally to this paper.*

Please address correspondence to:
Luca Cantarini, MD, PhD,
Research Centre of Systemic Autoinflammatory Diseases, Behçet's Disease and Rheumatology-Ophthalmology Collaborative Uveitis Centre, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Rheumatology Unit, Policlinico "Le Scotte", viale Bracci 1, 53100 Siena, Italy.
E-mail: cantariniluca@hotmail.com

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ABSTRACT

Monogenic autoinflammatory diseases (AIDs) are rare entities characterised by improper activation of the innate immune system. This in turn determines recurrent episodes of systemic inflammation characterised by fever, which is variously combined with a wide range of inflammatory manifestations involving the skin, joints, serous membranes, gastrointestinal tract, and central nervous system. As shown by research efforts conducted during the last decade, the eye is not exempt from the systemic inflammatory process and may be involved in almost all of the most frequent AIDs, with several distinct peculiarities. Ocular affections may severely impact patients' quality of life due to orbital pain, impairment of visual acuity, and/or long-term, sight-threatening complications. Consequently, in the context of a multidisciplinary team, ophthalmologists should be aware of ocular manifestations related to these disorders as they may have a dominant diagnostic weight in patients with a challenging presentation as well as a salient role in therapeutic choice in sight-threatening situations. This review describes a variety of aspects of ophthalmologic involvement in AIDs, looking at both well-recognised eye manifestations as well as rarely reported ocular presentations, with a particular focus on the recent literature.

Introduction

Autoinflammatory diseases (AIDs) embrace an expanding group of rare disorders characterised by seemingly unprovoked episodes of self-limited inflammatory attacks with no infectious agents, autoreactive T cells or autoantibodies observed. The pathogenesis of AIDs is hallmarked by genetic mutations of proteins involved in the modulation of the innate immunity and leading to the up-regulation of proinflammatory cytokines, especially interleukin (IL)-1β and tumour necrosis factor (TNF)-α (1, 2). The most common monogenic autoinflammatory disorders include familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD), idiopathic granulomatous diseases, and cryopyrin-associated periodic syndrome (CAPS) (Table I). CAPS includes three different clinical phenotypes: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic cutaneous and articular (CINCA) syndrome. These show increasing severity, with FCAS being the least severe and CINCA the most severe. From a clinical point of view, AIDs occur most often during childhood, however, the delayed onset of symptoms during adulthood has commonly been reported (3, 4). All AIDs are characterised by recurrent fever episodes and increased inflammatory markers variously combined with skin rash and inflammatory episodes affecting the joints, serous membranes, gastrointestinal tract, eyes, and central nervous system (5). Conversely, a complete wellbeing with normal acute phase reactants characterise inter-critical periods (6). However, AIDs can sometimes acquire a chronic course, especially in cases related to low-penetrance mutations, which often lead to adult-onset manifestations and incomplete or atypical phenotypes (7). Taken together, the rarity of AIDs and their relatively low knowledge among physicians along with the broad spectrum of possible clinical presentations and the need for a careful and correct genotype-phenotype correlation, may complicate the differential diagnosis in patients with suspected AIDs thus causing a delay in diagnosis (8-10).

Table I. Genetic and clinical features of the main autoinflammatory diseases.

AID	Gene/Locus	Inheritance	Protein	Fundamental clinical clues
FMF	*MEFV*/16p13.3	*AR*	Pyrin	Fever, serositis, arthralgia or arthritis generally affecting large joints, erysipela-like rash, amyloidosis in untreated patients
TRAPS	*TNFRSF1A*/12p13	*AD*	Tumour necrosis factor receptor 1	Fever, migrating erythematous skin rash, muscle pain in the form of fasciitis, conjunctivitis, periorbital oedema, arthralgia or arthritis, serosal involvement, amyloidosis
MKD	*MVK*/12q24	*AR*	Mevalonate kinase	Fever, polymorphous rash, arthralgia, abdominal pain, diarrhoea, lymph node enlargement, splenomegaly, aphtosis
MA	*MVK*/12q24	*AR*	Mevalonate kinase	Psychomotor retardation and growth delay, progressive cerebellar ataxia, dysmorphisms, vision deficits, MKD symptoms
FCAS	*NLRP3*/1q44	*AD*	Cryopyrin	Fever, cold-induced urticarial rash, conjunctivitis, arthralgia
MWS	*NLRP3*/1q44	*AD*	Cryopyrin	Fever, urticarial rash, conjunctivitis, episcleritis, arthralgia, sensorineural deafness, amyloidosis
CINCA	*NLRP3*/1q44	*AD*	Cryopyrin	Fever, urticarial skin rash, uveitis, papilledema, deforming arthritis mainly involving large joints, chronic aseptic meningopathy, sensorineural hearing loss, amyloidosis
Blau syndrome	*NOD2*/16q12.1-13	*AD*	Nucleotide-binding oligomerisation domain 2	Arthritis, skin rash, granulomatous inflammatory ocular involvement

AD: autosomal dominant; AID: autoinflammatory disease; AR: autosomal recessive; CINCA: chronic infantile neurologic cutaneous and articular syndrome; FCAS: familial cold autoinflammatory syndrome; FMF: familial Mediterranean fever; MA: mevalonic aciduria; *MEFV*: MEditerranean FeVer; MKD: mevalonate kinase deficiency; *MVK*: mevalonate kinase; MWS: Muckle-Wells syndrome; *NLRP3*: NACHT, LRR and PYD domains-containing protein 3; *NOD2*: nucleotide-binding oligomerisation domain 2; *TNFRSF1A*: tumour necrosis factor receptor super family 1A ; TRAPS: tumour necrosis factor-associated periodic syndrome.

Ocular involvement in AIDs may have distinct peculiarities (Table II). Figure 1 illustrates some of the most representative eye lesions of monogenic AIDs. Ocular affections may severely impact the quality of life due to orbital pain, impairment of visual acuity and/or long-term, sight-threatening complications. Hence, an increased awareness of AIDs is warranted among ophthalmologists in order to achieve an early diagnosis and optimal ocular management. The last decade has seen a number of interesting findings published on ocular involvement in AIDs (11-20). Herein, we review the current knowledge on this issue and provide a broad overview on the possible presentations of ocular affections in these rare diseases.

Familial Mediterranean fever

FMF is an autosomal recessive autoinflammatory disorder caused by mutations of the *MEFV* gene, encoding the pyrin protein. This immunoregulatory molecule, also known as marenostrin, is involved in the regulation of inflammation, cytokine production, and apoptosis. The cardinal phenotype of FMF is represented by recurrent episodes of fever generally lasting 48–72 hours, inflammation of one or more serosal membranes, a non-destructive arthritis usually involving one large joint of the lower limbs, and skin manifestations mostly in the form of erysipelas-like rash (21). Over time, this basilar clinical phenotype of FMF has been expanded with other clinical features including ocular involvement. The earliest paper on ophthalmologic affections was published in 1959 by Michaelson and colleagues, who described dotted lesions consistent with colloid bodies on routine funduscopic examination in 13 out of 23 patients; slit-lamp microscopy subsequently localised the lesions in the Bruch's lamina (22). Another patient displayed an ocular fundus with a solid-looking mulberry-like mass thought to originate from an adjacent colloid body (22). In 2014, a Turkish working group investigated retinal and choroidal thickness (CT) in 30 FMF children by measuring each subject's right eye at the fovea and horizontal nasal and temporal quadrants at 500 mm intervals to 1500 mm from the foveal using spectral-domain optic coherence Tomography (SD-OCT) (23). Although no significant differences were found between FMF patients and a control group, the authors highlighted the necessity to perform ocular evaluation during FMF attacks. In this regard, Gundogan *et al*. carried out a prospective case-controlled clinical study evaluating CT during acute attacks in 50 patients suffering from FMF (14). This study identified a significantly thicker choroid in FMF patients compared with healthy controls. Moreover, CT was positively correlated with inflammatory biomarkers, and especially C-reactive protein. The systemic inflammatory process during acute attacks and the following increase of vascular permeability, choroidal vessels enlargement and exudation may be responsible for the increase in CT with more impact during acute attacks rather than during symptom-free intervals (14). However, other authors have suggested the possible occurrence of confounding factors behind the increase of CT including the high body temperature during attacks and possible toxic consequences of treatment on choroidal tis-

Table II. Current knowledge on ocular involvement in monogenic autoinflammatory diseases.

Disease	First Author, year (ref)	Patients with ocular involvement/ Sample size	Mutations	Ocular description
FMF	Michaelson, 1959 (22)	14/24	NK	Fundal lesions resembling colloid bodies in Bruch membrane
	Erdurmus, 2014 (23)	30 pts	NK	No pathological changes in choroidal thickness during well-being periods
	Gundogan, 2016 (14)	50 pts	NK	Increased choroidal thickness during acute attacks
	Georgakopoulos, 2016 (27)	1/1	M694V/0	Acute posterior multifocal placoid pigment epitheliopathy
	Kosker, 2016 (16)	4/100	3 hom M694V 1 het M694V/M680I	Keratoconus
	Yazici, 1982 (28)	1/1	NK	Acute AU and episcleritis
	Yazici, 2014 (20)	6/6	NK	1 posterior scleritis, 2 AU, 1 IU, 2 PU Ocular complications: CME, epiretinal membranes, BK, cataract, glaucoma, and retinal ischaemia
	Petrushkin, 2015 (30)	1/1	NK	IU
TRAPS	Toro, 2000 (33)	11/25	NK	Conjunctivitis and PE
	Lachmann, 2014 (8)	71/158	NS (less likely to carry R92Q)	35 conjunctivitis, 32 PE, 20 periorbital pain
	Halligan, 2006 (35)	1/1	R92Q	Eyelid swelling and subepithelial, anterior stromal whorl-like deposits consistent with the concomitant Fabry disease
	Rösen-Wolff, 2001 (34)	3/3	2 C30R 1 T50M	Conjunctivitis, optic neuritis/papillitis
MKD	Prietsch, 2003 (39)	3/3	2 hom A334T, 1 het A334T plus 72insT*	Nuclear cataract, retinal dystrophy, and optic atrophy
	Simon, 2004 (40)	4/5	2 het V377I/W62X 1 het A334T/H20P 1 het A334T/W62X	Cataracts and progressive tapetoretinal degeneration
	Balgobind, 2005 (37)	1/1	Compound het 421insG* and A334T	RP
	Wilker, 2010 (41)	1/1	NK	RP-like retinopathy and punctate cataract
	Siemiatkowska, 2013 (18)	3 pts	1 hom A334T 2 het I268T/A334T	RP and posterior subcapsular cataract
	Kellner, 2017 (15)	2/2	het H20P/A334T	RP and early onset of cataract
	Durel, 2016 (38)	3/23 2/23 1/23	NS	3 conjunctivitis, 2 uveitis, 1 optic neuritis
CAPS	Dollfus, 2000 (43)	31 pts	NK	Papilledema, pseudopapilledema and optic atrophy; chronic AU, vitritis, vasculitis; BK, stromal infiltration, corneal neovascularisation, cataract.
	Rigante, 2010 (44)	1/1	NK	Post-inflammatory retinal dystrophy
	Terrada, 2011 (45)	1/1	D303N	Bilateral anterior, nummular, stromal keratitis; bilateral papilledema
	Hirano, 2015 (46)	1/1	D303N	Stromal keratitis and uveitis, pale optic disc, sheathed retinal arteries, yellowish deposits in the posterior pole
	Kawai, 2013 (47)	1/1	D303N	Conjunctival and episcleral injection plus bilateral optic disc swelling and retinal vascular sheathing around the optic disc
	Alejandre, 2014 (49)	3/3	R260W	Conjunctivitis, interstitial keratitis, uveitis
	Naz Villalba, 2016 (48)	1/1	T348M	Bilateral papilledema
	Oberg, 2013 (63)	2/2	R260W, T436A	Conjunctivitis, AU, bilateral papilledema and PanU
	Shakeel, 2007 (50)	1/1	A439V	AU
	Espandar, 2014 (51)	3/3	NK	Bilateral central stromal scarring with diffuse anterior stromal white blood cell infiltration
	Levy, 2015(7)	97/136	NS	Conjunctivitis, uveitis, optic nerve atrophy, cataract, glaucoma, papilledema
	Eroglu, 2016 (13)	6/14	I572F, Y570H, G569R, 2 patients with T436A, 1 genetically negative patient	Papilledema, optic atrophy, scleritis, severe iridoscleritis, uveitis
	Mehr, 2016 (10)	8/18	M662T, I572F, Y570C, T436N, R260W, 2 patients with T348M, 1 patient not tested	Papilledema
	Sobolewska, 2016 (19)	24/29	A439V in 15 patients, 9 genetically negative patient	Conjunctivitis, uveitis, ocular rosacea

Table II. *continued*

Disease	First Author, year (ref)	Patients with ocular involvement/ Sample size	Mutations	Ocular description
BS	Arvesen, 2017 (53)	1/1	R334Q	Granulomatous uveitis
	Milman, 2009 (58)	4/4	T605N	AU, bilateral PanU, chorioretinitis, scleritis, corneal opacities, retinal disruption
	Jimenez-Martinez, 2011 (56)	1/1	M513R	BK and PanU
	Raiji, 2011 (59)	1/1	D382E	Numerous small, white, corneal subepithelial ovoid opacities and conjunctival nodules and later a fulminant PanU
	Zeybek, 2015 (60)	1/1	P507S	Granulomatous AU
	Kim, 2016 (57)	2/2	H480R	AU, multiple mild subepithelial opacities on both eyes along with focal posterior synechia
	Jain, 2016 (55)	1/1	E667K	Right eye: non-granulomatous AU with vitreous haemorrhage Left eye: chronic AU, multiple iris granuloma, and complicated cataract
	Achille, 2016 (62)	1/1	het P268S/SNP5	Bilateral granulomatous PanU
	Carreño, 2015 (11)	9/9	6 het R334Q/wt 1 het Q809K/wt 1 het H520Y/wt 1 compound het E383D*/D390V	5 PanU, 3 AU, 1 IU Optic nerve and retinal features: pale optic disc in 6 eyes, indistinct margins in 6 eyes, sheathed optic disc vessels in 4 eyes, nodular excrescences in the peripapillary area in 13 eyes, hypopigmentation in 6 eyes and mixed hypo- and hyperpigmentation in 7 eyes
	Ebrahimiadib, 2016 (12)	6/6	E600A	Bilateral non-granulomatous PanU, bilateral retinal vasculitis, papillitis and scleritis
	Rosé, 2015 (17)	25/31	NS	AU, IU, 64% active vitreous inflammation, 18% active chorioretinitis, 5% active retinal vasculopathy. Complications: 64% synechiae, 55% cataract, 36% IOP, 23% BK, 14% macular oedema, 9% retinal detachment.

AU: anterior uveitis; BK: band keratopathy; BS: Blau syndrome; CAPS: cryopyrin associated periodic fever; CME: cystoid macular oedema; FMF: familial Mediterranean fever; het: heterozygous; hom: homozygous; IOP: increased intraocular pressure; IU: intermediate uveitis; KC: keratoconus; MKD: mevalonate kinase deficiency; NK: not known; NS: not specified for patients with ocular involvement; PanU: panuveitis; PE: periorbital oedema; PU: posterior uveitis; pts: patients; RP: retinitis pigmentosa; TRAPS: tumour necrosis factor receptor-associated periodic syndrome; wt: wild type.
*not found in Infevers (http://fmf.igh.cnrs.fr/ISSAID/infevers/).

sues (24, 25). In particular, a disruption of microtubules within retinal nerve fibre layer axons was manifested as a reduced birefringence on scanning laser polarimetry without abnormalities on retinal nerve fibre layer thickness measured by OCT (26).

An interesting case report presented the association of FMF with acute posterior multifocal placoid pigment epitheliopathy (APMPPE) in a patient with bilateral blurred vision and scotomata. As APMPPE was believed to be caused by an occlusive choroidal vasculitis, and given the increased frequency of vasculitis in FMF patients, the authors presumed there was a link between APMPPE and FMF (27).

FMF is also considered to be a predisposing factor for the development of keratoconus (KC), especially in patients carrying homozygous mutations of the *MEFV* gene. A possible interaction between FMF and KC was identified in 2016 by Kosker *et al*. who showed the prevalence of KC was higher in FMF patients than in a control group; 4 out of 100 FMF patients were affected by KC, whereas none of the 300 patients in the control group were affected (16). Furthermore, when compared with the highest prevalence reported in the literature, FMF was shown to be a predisposing factor for the development of KC, especially in patients carrying homozygous mutations (16).

With reference to uveal tract inflammation, Yazici and Pazarli described a patient with FMF who developed acute anterior uveitis in the left eye and episcleritis ten months later (28). Because of the two different forms of eye involvement, the authors were tempted to speculate a possible relationship between ocular inflammation and FMF. Following this, a case series on FMF patients with ocular involvement described 2 cases with anterior uveitis, 2 with posterior uveitis, 1 with intermediate uveitis, and 1 case with posterior scleritis (20). Cystoid macular oedema, epiretinal membranes, band keratopathy, cataract, branch retinal vein occlusion, neovascularisation, and glaucoma were also reported as ocular complications. It is noteworthy that 3 out of 6 patients presented a relapsing course, in line with the recurrent nature of FMF (20). However, 2 patients were also diagnosed with Behçet's disease (BD), as FMF and BD can coexist (29). A second case of intermediate uveitis was reported by Petrushkin *et al*. who described a female patient with FMF complaining from sudden floaters in the right eye (30). In any case, a careful diagnostic approach is warranted in patients with FMF and uveitis in order to rule out concomitant systemic disorders that may clinically overlap with FMF (20, 21).

TNF receptor-associated periodic syndrome

TRAPS, the most common among the autosomal dominant AIDs, is caused

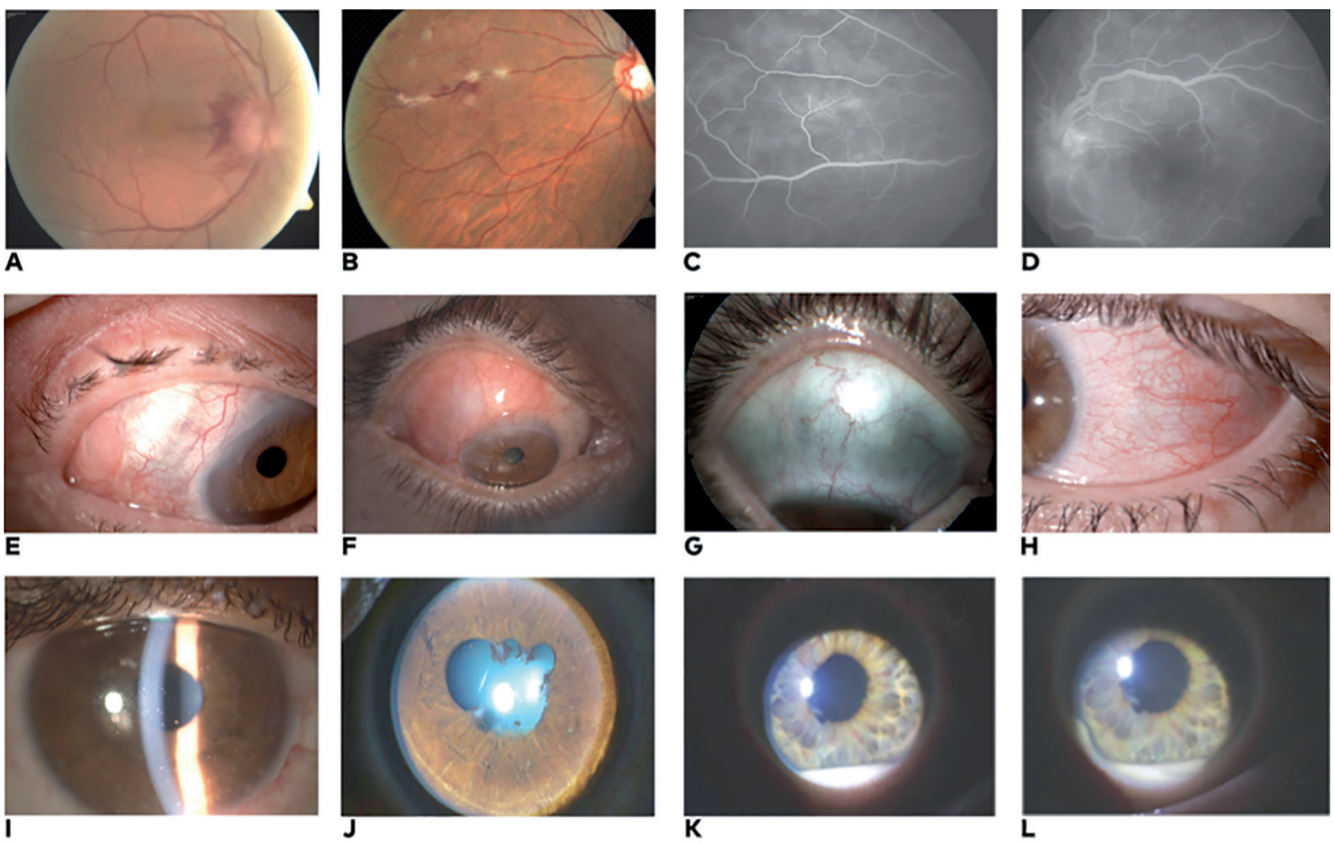

Fig. 1. Representative eye lesions in the monogenic autoinflammatory disorders.
(A) Swelling and peripapillary retinal oedema with haemorrhagic papillitis. **(B)** Retinal vasculitis. **(C-D)** Diffuse microvascular choriocapillaris vasculitis showing leakage of fluorescein during fluorescein retinal angiography. **(E-F)** Diffuse anterior necrotising scleritis resulting in scleromalacia. **(G)** with scleral thinning. **(H)** Diffuse anterior non-necrotising scleritis. **(I)** Granulomatous anterior uveitis. **(J)** Posterior irido-capsular synechiae. **(K-L)** Hypopyon in the anterior chamber. From Bascherini *et al*. 2015 (5).

by mutations in the *TNFRSF1A* gene, which encodes for the 55 kDa type-1 receptor of TNF-α. From a clinical point of view, this syndrome is characterised by recurrent inflammatory episodes lasting several weeks with a various combination of the following symptoms: fever, migrant erythematous rash, myalgia, lymphadenopathy, articular symptoms mainly represented by arthralgia, pleuritic and abdominal pain that may sometimes lead to exploratory laparotomy (31, 32). Ophthalmologic features have contributed to further expand the heterogeneous phenotype of TRAPS. Periorbital oedema and conjunctivitis are the most common ocular manifestations. In this regard, Toro *et al*. described conjunctivitis and/or periorbital oedema in 11 out of 50 TRAPS patients in a study conducted on 16 families (33). Accordingly, based on data from the Eurofever/EUROTRAPS international registry, the largest case series currently published on TRAPS patients identified periorbital oedema, periorbital pain, and conjunctivitis in 20%, 13%, and 22% of 158 subjects, respectively (8). Moreover, periorbital oedema tended to be significantly more common in paediatric patients as well as in adults with a disease onset during childhood. With regard to genotype-phenotype correlations, eye manifestations were less frequently encountered in patients carrying the R92Q low-penetrance mutation (8).

A sporadic case of optic neuritis/papillitis has also been reported in a German patient harbouring the C30R mutation who also developed fever, arthritis, skin rash myocarditis, and occasional diarrhoea (34).

An interesting association between TRAPS and Fabry disease was reported by Halligan and colleagues in which a 9-year-old boy presenting with symptoms consistent with TRAPS was found to carry the R92Q mutation (35). Among others, eyelid swelling was identified at physical examination, while an ophthalmologic examination revealed subepithelial, anterior stromal whorl-like deposits, which is a characteristic finding of Fabry disease. The authors suggested that the two genetic diseases may interact, potentially worsening the clinical phenotype (35).

Mevalonate kinase deficiency

The second most important autoinflammatory disorder with recessive inheritance is represented by MKD, determined by mutations in the *MVK* gene. The *MVK* gene encodes for mevalonate kinase, a crucial enzyme for the nonsteroidal isoprenoids biosynthesis, which in turn determines protein prenylation. The described metabolic defect triggers innate immunity hyperresponsiveness ultimately leading to recurrent multi-systemic inflammatory attacks classically characterised by fever, painful adenopathy, arthralgia, rash, and abdominal pain that may sometimes

require surgical examinations for possible acute abdomen. Currently, more than 200 sequence variants of the *MVK* gene have been associated with MKD, with most of them being single-nucleotide polymorphisms that lead to missense mutations. To date, the disease is considered as a phenotypic continuum of increasing severity according to the degree of residual enzymatic activity. It ranges from the milder form, hyper IgD syndrome (HIDS), to the most severe variant known as mevalonic aciduria (MA) (Table I). In its severest variant, the clinical phenotype may also be expressed by facial dimorphisms and central nervous system involvement including seizures, ataxia, myopathies, and psychomotor retardation (36).

Ophthalmologic features have contributed to MKD clinical heterogeneity as its clinical spectrum continues to expand (15, 18, 37-41). In a study by Prietsch *et al*., which investigated 3 MA patients with retinal dystrophy (RD), cataract accompanied RD in 2 siblings while optic atrophy was a supplementary finding in the third patient (39). Ocular involvement, along with ataxia and short stature, became predominant in patients surviving infancy, suggesting an age-dependent phenotype expression. For all these reasons, Prietsch *et al*. suggested ocular electrophysiology as an integral part of diagnostic evaluation in order to detect retinal disorders in patients with MA (39). Simon *et al*. also reported progressive blindness due to tapetoretinal degeneration and cataract in 4 patients with MKD (40).

As supported by several reports in the medical literature (15, 18, 37), retinitis pigmentosa (RP) is the most noteworthy ocular disease connected to MKD, and particularly to MA. Night blindness with funduscopic and full-field electroretinogram findings suggestive of RP was reported in a patient with MKD (37). In addition, RP-like retinopathy connected with MA was diagnosed on the basis of Goldmann visual field constrictions and full-field electroretinogram after a patient complained of nyctalopia and decreased peripheral vision; ophthalmologic evaluation also revealed findings fitting with punctate cataracts (41).

MKD can even be misdiagnosed as nonsyndromic RP, which might represent the presenting feature in such patients. In this regard, a proband of Dutch origin with RP was found to carry *MVK* mutations in a study by Siemiatkowska and colleagues; the *MVK* gene was subsequently tested in the patient's family and in a large cohort of patients with nonsyndromic, genetically unsolved RP (18). This study identified 3 subjects from 2 families with nonsyndromic RP who were found to have a mutation in the *MVK* gene. A detailed medical history revealed a mild form of MKD despite a significantly lowered mevalonate kinase activity, leading to misdiagnosis even among expert clinicians (18).

Recently, 2 brothers of German extraction with a compound heterozygous *MVK* mutation (H20P/A334T) were described in the first paper reporting an association of MKD and RP with early cataract development (15). As for the cases illustrated by Siemiatkowska and colleagues (18), a relatively mild phenotype was reported despite the severe effects of the A334T mutation, further suggesting the probable influence of additional genetic and environmental factors on disease manifestation.

On this basis, the currently proposed pathogenetic mechanism behind the non-random association between MKD and RP resides in an impaired isoprenylation, which probably interferes with macromolecules that are essential for the function of photoreceptors (37). It is noteworthy that most of the MKD patients with concomitant RP harbour the A334T (c.1000G>A) in exon 10 of the *MKV* gene (15, 18, 37, 39, 40), thus suggesting a potential genotype-phenotype correlation. Therefore, ophthalmological examination and instrumental ocular evaluation should be recommended for all patients with MKD.

The identification of cataract represents an interesting finding, which deserves attention in MKD patients (15, 39-41). A possible explanation for cataract could be a direct toxic effect of mevalonic acid rather than an osmotically-induced opacification. Indeed, young rat lenses cultured for up to 4 days in a medium containing mevalonic acid exhibited lens opacification and nuclear cataract within 1–2 days (42). In particular, water and sodium accumulated in the lenses, which lost soluble gamma crystallin proteins and potassium. Meanwhile, lenses lost the capacity to concentrate a potassium analogue (^{86}Rb), possibly due to a slow poisoning of the cation pump, an effect on membrane integrity or both (42).

Other ocular manifestations, including uveitis and optic neuritis, have been reported. An observational multicentre study aimed at classifying clinical and biological features of MKD in adulthood reported 3 patients with conjunctivitis, 2 of them with uveitis, and 1 case of optic neuritis (38).

Cryopyrin-associated periodic syndromes

CAPS represents a group of monogenic AIDs caused by *de-novo* or dominantly inherited gain-of-function missense mutations of the *NLRP3* gene. CAPS encompasses three overlapping syndromes sharing general anchor points and presenting an increasing disease severity that ranges from FCAS, the milder form, to CINCA, the most severe variant (13).

An increasing number of studies have explored the inflammatory eye involvement in patients with CAPS. In this regard, a relevant study on 136 CAPS patients has been recently published with the aim to retrospectively analyse demographic, genetic, and clinical data, and to investigate genotype-phenotype correlations (7). Ophthalmologic involvement was described in 71% of the patients. Specifically, 9 patients presented uveitis and 87 had conjunctivitis; in 16 cases, ocular manifestations were deemed severe and reported as impaired vision (n=8), optic nerve atrophy (n=6), cataract (n=4), and glaucoma (n=2). Although not statistically explored, severe ophthalmologic manifestations were more frequent in carriers of rare variants. Papilledema, reported as neurologic manifestation, was identified in 29 patients (7).

With respect to the clinical features of CINCA, a nonpruritic urticarial skin rash, generally occurring before the 6th month of life, is usually the present-

ing sign. The urticarial rash is often followed by articular manifestations responsible for joint and bone deformities over the long-term. Additional features may expand the protean spectrum with neurological abnormalities, including, chronic aseptic meningitis and sensory organ involvement with progressive sensorineural hearing loss and eye disease (43). Several types of ocular involvement have also been described in the CINCA syndrome. An international collaborative descriptive case-report study carried out on 31 patients found optic disc changes as the most common ocular finding in CINCA (43). Indeed, 84% of enrolled subjects presented with optic disc abnormalities including fluorescein angiogram-documented optic disc oedema in 13 out of 31 cases, papilledema in 7 out of 31 patients, and moderate to severe diffuse optic atrophy in 9 out of 31 cases. The involvement of the posterior segment was less frequent, with macular oedema found in 4 patients, retinal vasculitis in 3 patients, focal choroiditis in 1 patient, and vitritis in 4 patients. Anterior pole abnormalities were also described: 13% of patients exhibited dry eye and 42% displayed corneal involvement in the form of band keratopathy, stromal infiltration, corneal vascularisation, and cataract (43). On this basis, ophthalmologists should be familiar with the complex ocular profile of CINCA and constitute an integral part in the management team. Notably, complicated sight-threatening events, such as post-inflammatory retinal dystrophy, may severely impair visual acuity (44).

Corneal infiltrates were first reported by Terrada *et al*. in a patient with CINCA in which slit lamp biomicroscopy revealed bilateral anterior nummular stromal keratitis, and a fundus examination was evocative of bilateral papilledema (45). This last finding justified a permanent visual loss due to optic nerve fibre alteration despite a dramatic ophthalmologic improvement. Corneal infiltration has also been reported by Hirano *et al*. who described stromal keratitis and uveitis in a female patient with CINCA (46). Of note, both patients were found to harbour the D303N mutation (45, 46). This mutation was also found in a CAPS patient with conjunctival and episcleral injection in both eyes, and inflammatory cells in the anterior chamber; the patient also had bilateral optic disc swelling and retinal vascular sheathing around the optical discs (47).

A focus on ocular manifestations was carried out in a two-centred descriptive study, which described clinical and genetic features in a large cohort of Turkish paediatric patients with CAPS (13). Among the initial clinical findings, eye affections were identified in 6 out of 14 children. Three of these patients, classified as suffering from severe CAPS, exhibited papilledema and optic atrophy; 2 patients showed uveitis and the remaining patient had a severe iridoscleritis. One of the patients with uveitis had no mutations (13).

A recent study, which described epidemiological, clinical, and treatment characteristics of 18 Australian patients affected by CAPS, identified papilledema in 7 out of 8 CINCA patients and in 1 out of 8 patients diagnosed with MWS; this resolved after biologic treatment in 75% of cases (10). Similarly, bilateral papilledema was identified in a MWS patient, which improved after 3 months' treatment (48). Ophthalmological examination on 3 family members with MWS identified reticulated mid-stromal changes without corneal opacification in the proband and bilateral central corneal opacification in her mother and younger sister; an analysis of their personal history showed that they had also suffered from episcleritis, keratitis, and uveitis (49).

The first association of MWS with anterior uveitis was described in 2007 when Shakeel and Gouws reported a patient carrying the A439V mutation who complained of photophobia and blurred vision with keratic precipitates and hypopyon (50). The A439V mutation was also identified in a retrospective, observational cohort study specifically focused on ocular symptoms in 37 members of a 5-generation family (19). Eye involvement, represented by conjunctivitis followed by anterior uveitis, was the second most common finding after musculoskeletal affections; ocular rosacea was also described in 8 patients. Ophthalmologic manifestations were positively correlated with headache and skin rash and were significantly more frequent in genetically positive subjects than in their genetically negative relatives.

A severe form of ocular involvement may even occur in patients with FCAS, the mildest form of CAPS. An association between FCAS and keratitis was reported in 2014, with bilateral corneal scars and leukocyte infiltration on slit lamp examination described in 3 family members with FCAS (51).

Ocular involvement in MWS and FCAS can be as severe as that usually attributed to CINCA (48, 51). Indeed, careful ocular assessment may reveal serious issues, including interstitial keratitis and uveitis, which may necessitate the use of biologic agents to avoid ocular complications (48).

Blau syndrome

Both the familial and sporadic forms of the dominantly inherited granulomatous AIDs, defined as Blau syndrome (BS) and early-onset Sarcoidosis (EOS) respectively, are caused by gain-of-function mutations in the nucleotide oligomerisation domain *(NOD)-2* gene, mainly identified in the NATCH region (Table I) (3, 52). Typically, outbreaks occur during childhood and are characterised by non-caseating inflammatory granulomatous structures in the skin, joints, and uveal regions (3). Blurred vision, ocular pain, and photophobia are the most common ophthalmological complaints (53). BS carries a severe ocular morbidity (17) and is associated with a poor visual outcome (54). Patients harbouring the R334W and R334Q mutations seem to be particularly prone to developing panuveitis and have a worse visual prognosis (54). However, novel mutations reported in several case reports and small case series of patients with BS have also highlighted an important impairment of visual function (12, 53, 55-60).

The first report of the T605N mutation in the *NOD2* gene was described in 4 members of a Norwegian family with BS, who showed a wide range of eye involvement comprising bilateral panuveitis, anterior uveitis, scleritis, retinal disruption, and a case of corneal opacity (58).

Immunological features of BS at aqueous humour, vitreous and blood levels were initially analysed in 2011 in a BS patient with non-pruritic cutaneous rash and polyarthritis, who subsequently developed bilateral band keratopathy and panuveitis (56). The particular ocular milieu enriched in IL-6 and IL-8, along with a differential expression of chemokine receptors on T cells, were found to be related to the novel M513R mutation in the *NOD2* gene.

Numerous small and white corneal subepithelial opacities and conjunctival nodules were observed in a 2.5-year old female, previously misdiagnosed as an atypical juvenile idiopathic arthritis, who presented with a complicated ophthalmologic history (59). The patient later developed a fulminant refractory panuveitis. Based on the clinical presentation, genetic testing was performed which confirmed the diagnosis of BS and identified the D382E mutation, which had been reported only once previously in the literature (59).

Similarly, Zeybek *et al*. illustrated the case of a 5-year old male initially diagnosed with juvenile idiopathic arthritis and found thereafter to have BS in the light of granulomatous anterior uveitis revealed at an ophthalmologic examination; genetic testing determined the identification of a novel P507S mutation in the fourth exon of *NOD2* gene (60).

The mutational spectrum of BS has recently been expanded with further novel mutations identified. Specifically, 2 siblings who developed erythematous skin rashes and uveitis were found to carry the novel H480R mutation in the *NOD2* gene (57). Interestingly, although uveitis is generally the last BS manifestation to emerge (54, 56, 57, 59, 60), one of the siblings displayed an early onset ocular involvement. In addition, the *NOD2* common variant, P268S/SNP5, was identified as potentially associated with chronic uveitis in a study of 25 Italian patients suffering from inflammatory eye involvement compared with 25 healthy controls (61).

The first international, prospective cohort study of BS was a 3-year, multicentre, observational study designed to report baseline articular, functional, and ocular findings in 31 BS patients (17). A total of 25 patients (81%) had ocular involvement and all patients presented with anterior uveitis during their disease course. Posterior and intermediate uveitis were recorded in 72% and 52% of these patients, respectively, and active vitreous inflammation was identified in 64% of the cohort. Synechiae and cataract complications were identified in more than half the patients with anterior uveitis; ocular hypertension and band keratopathy were recorded in 36% and 23% of patients, respectively. Complications of posterior uveitis included macular oedema, optic atrophy, and retinal detachment (17).

Unlike skin rash, which is usually the earliest feature of BS, eye disease rarely constitutes the presenting symptom and is usually the last of the triad to emerge (54, 56, 57, 59, 60). However in selected cases, uveitis may precede other disease manifestations (55) or even represent the first sign of BS, which may be later diagnosed via genetic testing. As a case in point, genetic and molecular testing in a family with 7 members affected with refractory uveitis revealed a novel mutation converting glutamate to alanine in amino acid 600 (E600A) and an increased basal activity of *NOD2*, respectively (12). In 6 out of the 7 symptomatic family members, uveitis was the first disease manifestation and all of them suffered from panuveitis, although with a non-granulomatous type. It was postulated that in this subset of BS with adult onset and uveitis dominancy, the E600A mutation was responsible for a higher penetrance of uveitis and an early onset of ocular involvement (12). Together, these data suggest that atypical or incomplete forms of BS/EOS should be taken into account as possible diagnoses when facing chronic granulomatous uveitis (62).

Furthermore, other ocular structures, such as the optic nerve and retinal tissues, may be affected in BS. In a study which specifically examined optic nerve and retina in 17 eyes from 9 BS patients, indistinct disc margins were identified in 6 eyes, and optic nerve head pallor in 6 eyes; 4 eyes exhibited sheathed optic disc vessels (11). Hypopigmentation and a mixed hyper- and hypo-pigmentation accompanied by nodular excrescences in the peripapillary area were also noted in 6 and 7 eyes, respectively. The nodular aspect was related to the granulomatous nature of the inflammatory process and was also identified in patients with anterior uveitis. It was concluded that optic nerve abnormalities can be more often associated with BS than previously recognised and screening for mutations in the *NOD2* gene, in cases of characteristic retinal and optic disc changes, was recommended (11). Ocular inflammation and joint involvement represent the main clue that guide therapy, as early treatment is required to prevent articular sequelae and visual loss (12, 54, 59).

Conclusions

Considering their protean clinical spectrum, AIDs are rare entities that may present to a wide variety of care professionals, including ophthalmologists. On the basis of current knowledge, ocular involvement in AIDs should not be disregarded and ophthalmologists should be aware of ocular manifestations related to these disorders. Indeed, differential diagnosis may be challenging even among expert clinicians (9) and recognition of peculiar features may represent the turning point. In addition, ocular examination can reveal a serious involvement, such as uveitis and interstitial keratitis, even in the context of mild AIDs phenotypes (48, 51). In these cases, a prompt and careful multisystem workup including ocular examination can considerably improve the patients' prognosis and quality of life. To this extent, the ophthalmologist may have a dominant diagnostic weight and a salient role on therapeutic choice, thus bringing considerable benefits to disease evolution. However, as almost all available studies are small case series or present a retrospective design, many critical issues remain unsolved and further research on this topic is required to clarify unmet needs for strong evidence-based conclusions.

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