Clin Rheumatol (2015) 34:1171–1180
DOI 10.1007/s10067-015-2920-3

REVIEW ARTICLE

The protean ocular involvement in monogenic autoinflammatory diseases: state of the art

Vittoria Bascherini[1] · Carmela Granato[2] · Giuseppe Lopalco[3] · Giacomo Emmi[4] · Lorenzo Vannozzi[5] · Daniela Bacherini[5] · Rossella Franceschini[6] · Florenzo Iannone[3] · Annabella Salerni[7] · Francesco Molinaro[8] · Mario Messina[8] · Bruno Frediani[1] · Carlo Selmi[9,10] · Donato Rigante[11] · Luca Cantarini[1,12]

Received: 28 January 2015 / Revised: 15 March 2015 / Accepted: 17 March 2015 / Published online: 2 April 2015

Abstract Ocular involvement is frequent in the monogenic autoinflammatory disorders and generally occurs as spontaneously recurring inflammatory events at different ocular sites caused by the aberrant release of proinflammatory cytokines, mainly IL-1β. Over the past decade, we witnessed a significant growth of eye abnormalities associated with idiopathic granulomatous disorders, familial Mediterranean fever, tumor necrosis factor receptor-associated periodic syndrome, mevalonate kinase deficiency, and cryopyrin-associated periodic syndrome. The pathogenetic mechanisms of these disorders have shown the evidence of disrupted cytokine signaling, but the explanation for the heterogeneous ocular involvement remains to be elucidated. We herein review the monogenic autoinflammatory disorders affecting the eye, describing their main clinical features with specific regard to the ocular involvement, which can lead to decreased visual acuity and even blindness, if the primary disorder is undetected or left untreated.

Keywords Anakinra · Biologics · Canakinumab · Eye · Interleukin (IL)-1β · Uveitis

Introduction

Monogenic autoinflammatory disorders are an expanding group of diseases characterized by apparently spontaneous inflammation in the absence of autoantibodies or antigen-specific T cells, explaining the inflammatory features themselves [1, 2]. Different from autoimmune diseases, most of the abnormalities responsible for the clinical manifestations of these conditions are dependent on elective components of the innate immune

Vittoria Bascherini, Carmela Granato, Donato Rigante and Luca Cantarini contributed equally to this work.

✉ Luca Cantarini
cantariniluca@hotmail.com

[1] Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinic, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Siena, Italy

[2] Pediatrics Specialization, Second University of Naples, Naples, Italy

[3] Interdisciplinary Department of Medicine, Rheumatology Unit, Policlinic Hospital, University of Bari, Bari, Italy

[4] Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

[5] Department of Translational Surgery and Medicine, Eye Clinic, University of Florence, Florence, Italy

[6] Ophthalmology and Neurosurgery Department, University of Siena, Siena, Italy

[7] Institute of Ophthalmology, Università Cattolica Sacro Cuore, Fondazione Policlinico A. Gemelli, Rome, Italy

[8] Division of Pediatric Surgery, Department of Medical Sciences, Surgery, and Neuroscience, University of Siena, Siena, Italy

[9] Division of Rheumatology, Allergy, and Clinical Immunology, University of CA, Davis, USA

[10] Division of Rheumatology and Clinical Immunology, Humanitas Research Hospital, Rozzano, Milan, Italy

[11] Institute of Pediatrics, Università Cattolica Sacro Cuore, Fondazione Policlinico A. Gemelli, Rome, Italy

[12] Rheumatology Unit, Policlinico "Le Scotte", University of Siena, viale Bracci n. 1, 53100 Siena, Italy

system. These disorders generally result from an abnormal response to endogenous or exogenous factors, which results in an exaggerated activation of the inflammatory process, mainly mediated by the inflammasome, intracellular molecular platform coordinating the phylogenetically ancient response of the innate immune system leading to oversecretion of interleukin (IL)-1β and tumor necrosis factor (TNF)-α [3]. Within the family of monogenic autoinflammatory disorders, we mainly include idiopathic granulomatous diseases, familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), deficiency of mevalonate kinase (MKD), cryopyrin-associated periodic fever syndrome (CAPS, consisting of familial cold autoinflammatory syndrome or FCAS, Muckle-Wells syndrome or MWS, and chronic infantile neurologic cutaneous articular syndrome or CINCA syndrome), as summarized in Table 1.

In most patients, the disease onset is within the first year of life or during childhood, although in a subgroup of patients, the onset may occur in adulthood [4–7]. The severity of each inflammatory episode and any associated symptom as well as their frequency and duration may change significantly in the different disorders and even among individuals with the same condition [8]. Some clinical features are common, such as the presence of fever and periodic recurrence of systemic inflammatory episodes involving the skin, joints, serous membranes, lymph nodes, gastrointestinal tract, central nervous system, and eye [9–14]. The uncontrolled activation of the inflammatory system is accompanied by leukocytosis, thrombocytosis, and increased acute-phase reaction [15, 16]. The most ominous complication of these disorders is the onset of AA amyloidosis, especially when not pharmacologically controlled [9, 17, 18]. Ocular involvement may be quite common in the monogenic autoinflammatory disorders, starting with various clinical pictures, which if not searched for, detected, and treated promptly, might lead to decreased visual acuity and even blindness. Table 2 lists the ocular abnormalities observed in the medical literature related to different monogenic autoinflammatory disorders, and Fig. 1 depicts the most representative eye lesions in these conditions. Goal of this review is to survey the most relevant autoinflammatory disorders affecting the eye, describing their main clinical features and highlighting ocular involvement, which may occur in each of them.

Granulomatous disorders

The idiopathic autoinflammatory granulomatous disorders, including Blau syndrome and early-onset sarcoidosis, are characterized by subverted inflammatory response with formation of noncaseating granulomas in different organs [19, 20]. Both are determined by the mutation of the *NOD2/CARD15* gene, which normally encodes the NOD2 protein, and represent the autosomal dominant and sporadic forms of the disease, respectively [21, 22]. Blau syndrome usually begins in childhood and ordinarily affects the joints, skin, and eyes. Ocular involvement can be extremely severe, starting as granulomatous uveitis, often with a relapsing course and involving the anterior and/or posterior ocular segment with iridocyclitis, keratic precipitates, focal synechiae, vitritis, chorioretinitis, and sometimes optical neuritis, with risk of papilledema [23]. Clinically, Blau patients might have red eyes, ocular sensation of a foreign body, eye pain, photophobia, and blurred vision [24, 25]. Latkany et al. reported 16 patients from 8 different families affected by Blau syndrome, all with eye inflammation: 15 patients had panuveitis with multifocal choroiditis. Uveal inflammation was granulomatous and, in some cases, accompanied by keratic precipitates, with both anterior and posterior synechiae. Later, 11 patients developed cataract, 6 keratopathy bands, 6 optic disc edema, 2 epiretinal membranes, 6 cystoid macular edema, and 2 corneal scars. Retinal detachments, vitreous bleeding, iris neovascularization, retinal vasculitis, and ischemic optic neuropathy had also been noted [26]. In Blau syndrome, optic nerve and optic disc involvement are possible; as reported by Carreño et al., their study included 9 patients (and 17 eyes), all carriers of *NOD2* mutations. Of these, 6 eyes (37 %) had an optic papilla with indistinct margins; the papilla appeared pale in 6 eyes (37 %) and normal in 9 (56 %). Peripapillary pigmentation alteration was also identified: 6 eyes (37 %) showed an evident hypopigmentation and 7 (44 %) an alternating hypo/hyperpigmentation. Furthermore, it has been highlighted the presence of one or more nodules in the peripapillary area in 13 eyes (81 %) [27]. As suggested by Aróstegui et al., synechiae, recurrent bilateral conjunctivitis, and bilateral granulomas may represent other ocular signs related to Blau syndrome, whereas cataract and refractory intraocular hypertension are likely the consequence of treatment with topical corticosteroids over time [28].

Familial Mediterranean fever

FMF is the most common monogenic autoinflammatory disorder, caused by *MEFV* gene mutations, inherited with an autosomal recessive pattern, resulting in impairment of the pyrin protein, which can be prevented by continuous colchicine administration [29, 30]. The classic and most typical phenotype is characterized by recurrent acute episodes of fever, polyserositis, arthritis, and erysipelas-like erythema [31, 32]. Ocular involvement in FMF is not frequent. In 1959, Michaelson et al. were the first to describe eye involvement in the form of retinal bodies: in the tested group, consisting of 23 patients with recurrent polyserositis, 13 subjects (56 %) showed dotted lesions in both eyes, defined as retinal colloid-like bodies, with varying colors from porcelain-like white to yellowish, when examined with slit lamp. Eight patients (34 %) with a mean age of 32 years showed more numerous and widespread lesions, while in the remaining 5

Table 1 List of the main monogenic autoinflammatory disorders displaying a potential ocular involvement

Disease	FMF	TRAPS	MKD	FCAS	MWS	CINCAs	BLAUs
Gene (protein)	*MEFV* (pyrin)	*TNFRSF1A* (tumor necrosis factor receptor 1)	*MVK* (mevalonate kinase)	*NLRP3* (cryopyrin)	*NLRP3* (cryopyrin)	*NLRP3* (cryopyrin)	*NOD2/CARD15* (NOD2)
Chromosomal locus	16p13.3	12p13	12q24	1q44	1q44	1q44	16q12.1-13
Inheritance	AR	AD	AR	AD	AD	AD	AD
Age at onset	Pediatric age	Adolescence or adulthood	First infancy	First infancy	First infancy	First infancy	First infancy
Distinctive features	Diffuse in Sephardic Jewish, Armenian, Arab, and Turkish populations; amyloidosis in colchicine-resistant and untreated patients	Periorbital edema and inflammatory attacks having a length of 1–3 weeks	Attacks triggered by vaccinations or infections	Short duration of each attack	Sensorineural hearing loss	Presentation of the rash in the neonatal period, chronic meningitis with papilledema, hearing loss, and deforming knee osteoarthropathy	Symmetrical granulomatous arthritis, red macular-papular-nodular rash, and granulomatous panuveitis
Treatment	Colchicine, anakinra, and canakinumab	Corticosteroids, etanercept, anakinra, canakinumab, and tocilizumab	NSAIDs, corticosteroids, and anakinra	Cold avoidance, anakinra, rilonacept, and canakinumab	Anakinra, rilonacept, and canakinumab	Anakinra, rilonacept, and canakinumab	NSAIDs corticosteroids, TNF-α inhibitors, immunosuppressive agents, thalidomide, anakinra, and canakinumab

AD autosomal dominant, *AR* autosomal recessive, *BLAUs* Blau syndrome, *CINCAs* chronic infantile neurologic cutaneous articular syndrome, *FCAS* familial cold autoinflammatory syndrome, *FMF* familial Mediterranean fever, *MKD* deficiency of mevalonate kinase, *MWS* Muckle-Wells syndrome, *NSAIDs* nonsteroidal anti-inflammatory drugs, *TRAPS* tumor necrosis factor receptor-associated periodic syndrome

Table 2 Overview of the medical literature regarding ocular involvement in the monogenic autoinflammatory disorders

Disease	First author (year, reference)	Number of pts. with ocular involvement	Mutation	Origin	Clinical and laboratory features	Treatments
FMF	Michaelson 1959 [33]	13/23	Unknown	Jewish	Retinal colloid-like bodies	Unknown
	Yazici 1982 [34]	1/1	Unknown	Armenian	Anterior uveitis and episcleritis	NSAIDs, topical and systemic CCs, and colchicine
	Yazici 2014 [35]	6/6	Unknown	Unknown	Posterior scleritis, anterior uveitis, intermediate uveitis, and posterior uveitis	Topical and systemic CCs, methotrexate, cyclosporine, colchicine, and surgery
	Hirsh 1990 [36]	1/1	Unknown	Sephardic Jewish	Panuveitis and retinal detachment	Colchicine and topical and systemic CCs
	Finsterer 2002 [37]	1/1	M694V	Turkish	Blurred and double vision, ptosis, and ophthalmoparesis	Unknown
	Lossos 1993 [38]	2/2	Unknown	Jewish-Moroccan and Jewish-Kurdish	Retrobulbar optic neuritis	Systemic CCs and colchicine
TRAPS	Toro 2000 [52]	11/25	Unknown	Unknown	Conjunctivitis, eye redness and pain, and periorbital edema	Unknown
	Kümpfel 2007 [53]	4/6	R92Q	German, Croatian, Arabian, and Greek	Periorbital edema and conjunctivitis	Unknown
	Minden 2004 [54]	2/2	T50K	Unknown	Recurrent conjunctivitis, periorbital edema, and optic neuritis	Systemic CCs, chlorambucil, azathioprine, methotrexate, and etanercept
	Rösen-Wolff 2001 [55]	3/3	T50M C30R	German	Conjunctivitis, optic neuritis, and papillitis	Systemic CCs, immunoglobulins, cyclosporine, chlorambucil, and methotrexate
FCAS	Espandar 2014 [67]	3/3	Unknown	Unknown	Ocular pain, photophobia, keratitis, and iritis	Topical CCs and canakinumab
MWS	Kitley 2010 [71]	8/13	T348M A439T R260W	British (1 patient) and unknown (others)	Optic disc pallor, bilateral conjunctivitis, and papilledema	Canakinumab
	Gorovoy 2013 [73]	1/1	Unknown	Unknown	Chronic bilateral iritis and keratitis	Topical CCs, surgery, and anakinra
	Shakeel 2007 [74]	1/1	A439V	Unknown	Anterior uveitis, hypopyon, conjunctivitis, photophobia, and blurred vision	Unknown
CINCAs	Dollfus 2000 [82]	31/31	Unknown	Argentine, Canadian, Finnish, French, English, German, Italian, Dutch, Portuguese, American, and Slovak	Pseudopapilledema, optic disc edema/atrophy, corneal abnormalities, chronic anterior uveitis, and posterior uveitis	Topical CCs
	Sadiq 1996 [83]	1/1	Unknown	Caucasian	Anterior uveitis	Cyclosporine
	Terrada 2011 [85]	1/1	D303N	Caucasian	Nummular bilateral keratitis and papilledema	Anakinra
	Teoh 2007 [86]	1/1	Unknown	Unknown	Bilateral panuveitis and hypopyon	Methotrexate, topical and systemic CCs, etanercept, and anakinra
	Rigante 2010 [87]	1/1	F573S	Italian	Chorioretinitis, papilledema, and retinal dystrophy	Systemic CCs, NSAIDs, etanercept, colchicine, and anakinra
	Khemani 2007 [88]	1/1	F309S	Indian	Retinal vasculitis and conjunctival nodules	Systemic CCs and azathioprine
	Russo 2001 [89]	2/2	Unknown	Unknown	Retinal vasculitis, papilledema, and corneal ulcers	Systemic CCs, NSAIDs, and azathioprine
BLAUs	Latkany 2002 [26]	16/16	Unknown	Unknown	Panuveitis, multifocal choroiditis, anterior uveitis, retinal vasculitis, and ischemic optic neuropathy	Systemic CCs, cyclosporine, methotrexate, etanercept, and mycophenolate mofetil

Table 2 (continued)

Disease	First author (year, reference)	Number of pts. with ocular involvement	Mutation	Origin	Clinical and laboratory features	Treatments
	Carreño 2014 [27]	9/9	R334W R334Q Q809K E338D D390V H520Y	Spanish	Panuveitis, anterior uveitis, intermediate uveitis, and posterior uveitis	Topical and systemic CCs, methotrexate, mycophenolate mofetil, and TNF-α inhibitors
	Aróstegui 2007 [28]	7/12	R334W R334Q C495Y R587C	Spanish	Panuveitis, anterior uveitis, recurrent conjunctivitis, and granulomas	Topical and systemic CCs, NSAIDs, salicylic acid, methotrexate etanercept, cyclosporin, and anakinra + mycophenolate mofetil
	La Torre 2015 [23]	1/1	E383G	Italian	Bilateral panuveitis	NSAIDs, topical and systemic CCs, methotrexate, and TNF-α inhibitors
MKD	Prietsch 2003 [60]	3/3	A334T	Unknown	Nuclear cataract, retinal dystrophy, and optic atrophy	Vitamin E, A, and C
	Balgobind 2005 [61]	1/1	A334T	Caucasian	Retinitis pigmentosa	Unknown

BLAUs Blau syndrome, *CINCAs* chronic infantile neurologic cutaneous articular syndrome, *CCs* corticosteroids, *FCAS* familial cold autoinflammatory syndrome, *FMF* familial Mediterranean fever, *MKD* deficiency of mevalonate kinase, *MWS* Muckle-Wells syndrome, *NSAIDs* nonsteroidal anti-inflammatory drugs, *TRAPS* tumor necrosis factor receptor-associated periodic syndrome

patients, the lesions were fewer in number and more isolated [33]. In 1982, Yazici and Pazarli reported the case of a woman suffering from FMF with anterior uveitis, which subsequently evolved over time into an episcleritis [34]. In a case series reported in 2014, ocular involvement has been reported in 6 FMF patients: 4 of them, males, had a bilateral involvement; the clinical course of ocular disease was acute in 1 patient, relapsing in 3 patients, and chronic in the other 2 (33.3 %), who finally developed an anterior uveitis, though 1 of these patients was also diagnosed with Behçet disease. Pulsed methylprednisolone has been used in association with immunosuppressant drugs and colchicine, but despite aggressive treatment, some patients developed cataract, glaucoma, and keratopathy bands; cystoid macular edema was demonstrated in 2 patients manifesting a posterior uveitis with vitritis and retinal vasculitis, though Behçet disease was also diagnosed in 1 [35]. Hirsh et al. also historically reported another case of bilateral panuveitis in a young Jewish man, who developed a rhegmatogenous retinal detachment [36]. In 2002, Finsterer and Stöllberger reported a patient diagnosed with FMF who developed headache, diplopia, blurred vision, ophthalmoparesis, and peripheral paralysis of the facial nerve: given the rare involvement of central and peripheral nervous system in FMF, the authors speculated that these events were due to secondary amyloidosis or cerebral vasculitis [37]. Involvement of the central nervous system has also been found by Lossos et al., who reported 2 patients with optic neuritis and visual impairment [38].

TNF receptor-associated periodic syndrome (TRAPS)

TRAPS is an autosomal dominant disorder caused by mutations in the *TNFRSF1A* gene encoding the 55-kDa receptor of TNF [39]. Although phenotypes and clinical manifestations are highly variable, this syndrome is usually characterized by the presence of febrile episodes of variable length from a few days to a few weeks [40–45] associated with protean clinical signs, such as abdominal pain, myalgia, rash, arthralgia, or arthritis [46, 47]. In recent years, the range of potential manifestations has expanded, as a result of different reports of pericarditis, sacroiliitis, meningitis, encephalitis, and recurrent psychosis [48–51]. Conjunctivitis and periorbital edema are the most frequent ocular manifestations that occur during acute episodes of illness. Toro et al. reported data relating to a group of 25 patients suffering from TRAPS: 11 subjects (44 %) had ocular involvement in the form of conjunctivitis, characterized by eye redness and pain, and periorbital edema [52]. In the medical literature, there are cases of ocular involvement in patients with TRAPS and multiple sclerosis. Kümpfel et al. reported that among patients with multiple sclerosis, 6 (3 %) were carriers of the mutation R92Q and had symptoms consistent with the diagnosis of TRAPS: 2 of these showed eyelid edema and 2 recurrent conjunctivitis [53].

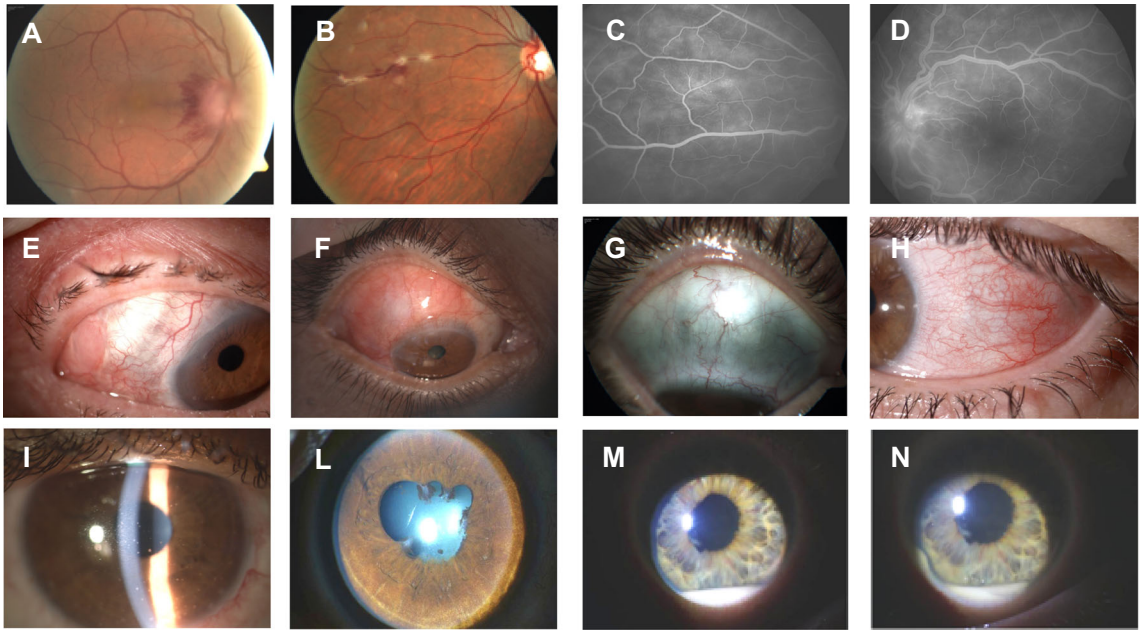

Fig. 1 Representative eye lesions in the monogenic autoinflammatory disorders: **a** swelling and peripapillary retinal edema with hemorrhagic papillitis, **b** retinal vasculitis, **c**, **d** diffuse microvascular coriocapillary vasculitis showing leakage of fluorescein during fluorescein retinal angiography, **e**, **f** diffuse anterior necrotizing scleritis resulting in scleromalacia (**g**) with scleral thinning, **h** diffuse anterior non-necrotizing scleritis, **i** granulomatous anterior uveitis, **l** posterior iridocapsular synechiae, and **m**, **n** hypopyon in the anterior chamber

In 2004, Minden et al. reported a young boy and his sister carrying the T50K mutation in the exon 3 of the *TNFRSF1A* gene that had recurrent conjunctivitis and periorbital edema since childhood. In addition, brain magnetic resonance imaging studies in a young woman detected small demyelinating supratentorial lesions; after 20 months of treatment with the anti-TNF etanercept, this subject developed unilateral optic neuritis with new demyelinating lesions [54]. An interest charged to the peripheral nervous system is also reported by Rösen-Wolff et al. in a woman with the C30R mutation, who developed optic neuritis and papillitis, which regressed spontaneously [55].

Mevalonate kinase deficiency (MKD)

MKD is an autosomal recessive disorder caused by mutations in the *MVK* gene [56], which encodes the mevalonate kinase enzyme involved in the ATP-dependent phosphorylation of mevalonic acid to 5-phosphomevalonate: the different mutations known to date are all responsible for a decreased enzymatic activity, resulting in overproduction of proinflammatory isoprenoids, decreased cholesterol synthesis, and accumulation of mevalonic acid in the plasma and in the urine of affected individuals [57]. The disease usually occurs in the first year of life with febrile episodes that occur every 4–6 weeks and usually last 3–7 days, accompanied with headache, abdominal pain, skin rash, vomiting, diarrhea, oral ulcerations, arthralgia, and even arthritis; the absolute deficiency of the enzyme leads to mevalonic aciduria, characterized by dysmorphic signs, psychomotor retardation, and also recurrent febrile crises [58, 59]. In the medical literature, there are several cases of ocular involvement in the course of MKD. Prietsch et al. reported 3 patients with mevalonic aciduria with nuclear cataract and retinal dystrophy: 1 of these patients had also a moderate optic atrophy [60]. Balgobind et al. described a child with MKD and night blindness with evidence of retinitis pigmentosa [61], a disorder characterized by visual field loss, often associated with many metabolic diseases [62]. The concomitant presence of retinitis pigmentosa in patients with MKD suggests a peculiar vulnerability of retinal photoreceptors to metabolic abnormalities and/or cytokine imbalance, as the retina produces mainly non-sterol isoprenoids, essential for the post-translational protein isoprenylation [63]. The impairment of isoprenoid biosynthesis might interpose with the proper functioning of proteins essential for photoreceptor activity [64].

Cryopyrin-associated periodic fever syndrome (CAPS)

CAPS is a group of monogenic autoinflammatory disorders determined by the mutation of the *NLRP3* gene, coding for cryopyrin: there are three forms of CAPS, distinguished according to the variable severity of the clinical picture.

Familial cold autoinflammatory syndrome (FCAS)

FCAS is the milder phenotype of this syndrome, which presents in familial aggregations and usually occurs within the

first months of life, characterized by recurrent inflammatory episodes triggered by the exposure to cold or temperature changes. Symptoms are fever, urticaria-like rashes (poorly responsive to antihistamines), arthritis or diffuse joint pain, headache, and chronic fatigue [65, 66]. Ocular manifestations are mild and mainly represented by inflammation of the conjunctiva. In 2013, Espandar et al. reported 3 patients with recurrent episodes of red eyes and iritis. In all cases, slit lamp examination showed the presence of bilateral corneal scars and widespread infiltration of leukocytes. Although treatment with prednisolone allows the resolution of eye involvement in all patients, therapy with IL-1 antagonists such as canakinumab may be useful to reverse the systemic and ocular signs of the disorder [67].

Muckle-Wells syndrome (MWS)

MWS is the CAPS phenotype of intermediate severity: the disease appears in childhood, but in addition to the typical symptoms of FCAS, MWS patients may have episcleritis and sensorineural hearing loss [68–70]. Although the neurologic involvement is best known in patients with CINCA syndrome, 13 patients with MWS and central nervous system involvement have been reported in the medical literature; in particular, 2 of these showed optic disc pallor and 6 a frank papilledema [71]. Recently, Kawai et al. reported a 35-year-old CAPS patient carrying a c.907G>A heterozygous mutation and presenting with periodic fever, urticaria-like skin rash, arthralgia, headache, and eye redness; slit lamp examination showed conjunctival and episcleral injection in both eyes, and ophthalmoscopy revealed bilateral optic disc swelling and retinal vascular sheathing around the optic discs [72]. In 2013, Gorovoy et al. reported the case of a woman suffering from MWS with a chronic bilateral iritis and progressive corneal opacification, because of which she underwent keratoplasty; the histological analysis showed a chronic stromal keratitis with epithelioid histiocytes in the posterior stroma and focal calcification at the level of the Bowman's capsule [73]. Uveitis can also be found in MWS, especially in the anterior segment, as reported by Shakeel and Gouws, which readily responds to conventional treatment [74].

Chronic infantile neurologic cutaneous articular syndrome (CINCA)

CINCA syndrome is the most severe among the clinical expressions of CAPS [75, 76], generally associated with sporadic *NLRP3* mutations [77]. The onset is in the first days of life with widespread urticaria-like rash, not itchy like in the classical urticarial rashes [78]. Then, the most relevant manifestations are cerebral atrophy, with increased intracranial pressure due to chronic aseptic meningitis and deforming osteoarthropathy, especially affecting large joints [79–81]. Various ocular manifestations have been described in CINCA syndrome. An international study performed on 31 patients reported abnormalities of the optic disc (found in 83 % of patients) as the most common ocular manifestations: 13 out of 31 patients had optic disc edema, 9 optic atrophy, and 7 pseudopapilledema. In 27 % of cases, visual acuity was decreased unilaterally or bilaterally. Corneal abnormalities as keratopathy, neovascularization, and opacification were observed in 42 % of subjects, and 5 of these also showed chronically red eyes. The posterior pole was found to be the less frequently involved segment (only in 19 % of cases: vitritis in 4, macular edema in 4, retinal vasculitis in 3, and focal choroiditis in 1) [82]. In a case of chronic anterior uveitis, without any posterior synechiae, therapy with cyclosporine has allowed the resolution of the inflammatory picture [83]. During the acute phases of the disease, infiltration with white blood cells can be observed in the sites of inflammation (retina, optic nerve, and pars plana), and a number of polymorphonuclear cells can be revealed by means of vitreous humor cytological analysis [84]. As reported by Terrada et al., corneal involvement can be evident in patients with CINCA syndrome, in the form of nummular anterior keratitis, which might improve after treatment with the IL-1 receptor antagonist anakinra [85]. The efficacy of treatment with IL-1 inhibitors in improving ocular symptoms has also been reported by Teoh et al., who described the case of a 4-year-old child with bilateral recurrent panuveitis unresponsive to methotrexate and etanercept, in whom anakinra was clearly successful [86]. A case of post-inflammatory retinal dystrophy has been described in a 10-year-old child with CINCA syndrome, who presented chorioretinitis and convergent squint in the first months of life, and then papilledema [87]. In 2007, Khemani and Khubchandani reported the first case of CINCA syndrome in India: a 7-year-old girl carrying the de novo F309S *NLRP3* mutation with history of several episodes of retinal vasculitis and conjunctival nodules, in whom treatment with azathioprine blocked the progression of eye damage and resulted in the stabilization of visual acuity [88]. Another case of retinal vasculitis with papilledema regressed after treatment with azathioprine, while pale optic disc and numerous corneal ulcers, framed in the context of CINCA syndrome, were successfully treated with prednisone and ibuprofen [89].

Conclusions

Mutations in different genes involved in the control of inflammation and in the cytokine repertoire have been associated to "autoinflammation," discriminating a new category of conditions from autoimmune diseases named monogenic autoinflammatory disorders, in which variable involvement of other tissues, including joints, skin, gastrointestinal tube, and serosal membranes, can be found. Ocular signs in

autoinflammatory disorders are frequently observed and might be severe, causing visual loss, particularly in Blau syndrome and CINCA syndrome, and requiring aggressive specific therapies. Further research should continue to enhance the understanding of the genetics and causes of these disorders, and result in improvements in their diagnosis and treatment.

Take-home messages

- Monogenic autoinflammatory disorders result in an exaggerated activation of the inflammatory process leading to oversecretion of different proinflammatory cytokines, such as interleukin-1b and tumor necrosis factor-α.
- Eye involvement may be commonly observed in some monogenic autoinflammatory disorders like Blau syndrome and CINCA syndrome and is heterogeneous in terms of clinical expression.
- Eye involvement, when untreated, may represent a potentially severe event with long-term complications and even risk of blindness.
- The first common step in managing ocular disease in autoinflammatory disorders is the topical application of corticosteroids and/or systemic administration of corticosteroids, whereas the use of immunosuppressant drugs is advocated in the case of reactivation and/or additional complications.
- Biologic agents might act as new and potent tools in the armamentarium of therapies available for refractory eye involvement in patients with monogenic autoinflammatory disorders.

Disclosures None.

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