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ORIGINAL ARTICLE

Long-Term Visual Outcome of Patients with Blau Syndrome

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ABSTRACT

Purpose: To document the long-term visual outcomes in patients with Blau syndrome.
Methods: A retrospective institutional cohort study was conducted, and 13 patients with genetically confirmed Blau syndrome were included. Demographic and clinical data were collected from standardised medical charts. Baseline was defined as the first detected uveitis and data were recorded onwards at intervals of 1, 3, 5, 10, 15 and 20 years.
Results: Anterior uveitis was the most common classification at baseline (57.1%). Among patients with documented uveitis lasting 10 years or more, all of them developed panuveitis. Median logMAR visual acuity at baseline was 0 (range −0.5; 0.7), 0.19 (range 0; 1.5) at year 5, and 0.7 (range 0.1 – no perception of light) at year 20, as recorded in 13, 16, and 10 eyes, respectively. All patients received treatment with topical and oral steroids, and multiple systemic immunosuppressants including biologics. Disease control, defined as having cells <1+ in both eyes and using topical steroid eye drops less than twice daily, was achieved in 14.3% to 37.5% of patients at the different time points. Cataract surgery was performed in 12 eyes of 8 patients, 3 eyes of 3 patients necessitated glaucoma surgery, and 4 eyes of 4 patients required surgery for retinal detachment.
Conclusion: Uveitis associated with Blau syndrome commonly leads to severe, chronic panuveitis, requiring long-term systemic immunosuppression. Early diagnosis and timely initiation of biologics may prevent significant visual impairment.

Blau syndrome is a rare monogenic autoinflammatory disease, caused by *de novo* or dominantly inherited *gain-of-function* (GoF) mutations in the *NOD2* gene.[1] The Nod2 protein plays a relevant role in the regulation of innate immune response, and its constitutive activation due to GoF mutations causes an upregulation of NF-κB and induction of inflammation.[1,2] The disorder (also referred to as Blau-Jabs syndrome) typically commences in early childhood (<4 years-old) with a clinical triad of non-caseating granulomatous dermatitis, chronic and symmetric oligopolyarthritis, and uveitis.[3–5] The main characteristics of Blau syndrome-associated uveitis have been described in several cross-sectional case series.[6,7] However, a limitation of reports to date is the paucity of longitudinal data with long-term visual outcome and treatment outcomes. In this study, we aimed to quantify the long-term visual prognosis in patients with Blau syndrome, the prevalence of complications, surgical intervention, and outcomes of administered treatments.

Methods

A retrospective, longitudinal cohort study was conducted at Bristol Eye Hospital, NHS University Hospitals Bristol and Weston, United Kingdom. The study included paediatric and adult patients diagnosed with Blau syndrome and genetically confirmed by *NOD2* testing between 2010 and 2022. Patients with systemic diseases known to cause uveitis (i.e. juvenile idiopathic arthritis [JIA], Behçet's disease, demyelinating disease, and others) were excluded from analysis. As the timing and duration of follow-up varied among patients and we aimed to longitudinally assess the impact of ocular involvement, "baseline" was defined as the time of first diagnosis of uveitis (at Bristol Eye Hospital, or elsewhere). Available clinical data were collected from medical records with a standardized form and categorized into standard time intervals, including baseline, 12 months, 3, 5, 10, 15 and 20 years. The requirement for ethics committee approval was waived by the Institutional Review Board.

Demographic data, such as age at disease onset, gender, comorbidities, and familial history of autoinflammatory or autoimmune disease, were collected. Clinical data at each time point included visual acuity (logMAR), laterality of uveitis, anatomical classification, and course of the uveitis according to the criteria of the SUN working group,[8] and clinical features. The main outcome measures for assessing visual

prognosis included best-corrected visual acuity (logMAR >0.3 [worse than 612] or >1.0 (660 or worse]) in each eye, presence of macular oedema, and need for surgical interventions such as cataract and glaucoma treatment. Assessment of anterior chamber disease activity was recorded following SUN guidelines,[8] and vitritis extent documented using the BIO score.[9] The presence of cystoid macular oedema (CMO) and disc swelling was assessed clinically and by optical coherence tomography (OCT, Topcon 3D-OCT 1000, Topcon Medical Systems). Ocular hypertension was defined as intraocular pressure exceeding 21 mmHg without evidence of glaucomatous optic nerve changes. An intraocular pressure below 6 mmHg was noted as ocular hypotony. Other ocular complications including band keratopathy, optic nerve atrophy (disc pallor), and choroidal neovascular membranes occurring during follow-up were also recorded. All data were recorded in a database and subjected to descriptive analysis.

Results

A total of 14 individuals carrying pathogenic *NOD2* variants causing Blau syndrome were initially identified (see Supplementary Tables S1 and S2 for genetics data). One female was excluded from the analysis due to being an asymptomatic carrier, as she did not exhibit any features of skin, joint or ocular inflammation at screening at the ages of 3, 4 and 6 years old. The remaining 13 individuals (26 eyes) were diagnosed with Blau syndrome and consisted of 5 patients (38.5%) across 3 unrelated families, and 8 sporadic cases (61.5%). The clinical data were stratified based on the timing of reviews relative to baseline. Detailed ocular data were available for 7 patients (14 eyes) at baseline, and for 6 patients (12 eyes), 8 patients (16 eyes), 7 patients (14 eyes), 5 patients (10 eyes), 6 patients (12

eyes), and 5 patients (10 eyes) at year 1, 3, 5, 10, 15, and 20 following first detection of uveitis, respectively (see Table 1).

Out of the 13 patients, 8 (61.5%) were males, and 5 (38.5%) were females. The median age at the onset of systemic symptoms was 18 months (range 3–48 months). In 4 patients, uveitis was diagnosed concurrently with systemic symptoms. In the remaining 9 patients, the diagnosis of uveitis followed the onset of systemic features by a median of 58 months (range 13–193 months). Patients had initially been diagnosed with JIA (813; 61.5%) or sarcoidosis (513; 38.5%). The appearance of multifocal chorioretinal and peripapillary lesionsscars that developed during follow-up of refractory uveitis and/or a family history of disease had prompted genetic analysis. In two patients, corneal subepithelial opacities were observed in both eyes after the onset of systemic symptoms, but uveitis was detected 40 and 60 months later, respectively. The anatomical subtype and laterality of uveitis are presented in Table 2. Most patients seen at uveitis onset (4 out of 7; 57.1%) presented with anterior uveitis. The proportion of panuveitis steadily increased, and after 10 years of disease evolution, all cases were classified as panuveitis.

Visual acuity

Table 3 displays visual acuity data of this cohort. A decline in visual acuity was observed from baseline (median 0; 1 in 11 eyes [9.1%] logMAR >0.3) throughout year 10 (median 0.2; 4 in 10 eyes [40%] logMAR >0.3) to year 20 (median 0.7; 8 of 10 eyes [80%] logMAR >0.3). Only 2 of 5 patients with disease duration of 20 years had visual acuity in the better eye exceeding logMAR 0.3 (Snellen 612). One patient developed unilateral phthisis without light perception 11 years following onset of uveitis.

Table 1. Overview of available data of cohort at different time points (B = baseline; yr = year).

	B	Yr 1	Yr 3	Yr 5	Yr 10	Yr 15	Yr 20
1	o	o	o				
2	o	o	o	o			
3	o	o	o	o	o	o	
4	o	o	o	o			
5	o						
6			o	o			
7						o	o
8	o	o	o	o	o		
9			o	o	o	o	o
10						o	o
11	o	o	o	o	o		
12						o	o	o
13						o	o

Table 2. Anatomical subtype and laterality of Blau syndrome associated uveitis (T: time point; N: number of patients).

		Anatomical subtype of uveitis			Laterality	
t	N	Anterior	Intermediate	Panuveitis	Unilateral	Bilateral
Baseline	7	4 (57.1%)	2 (28.6%)	1 (14.3%)	1 (14.3%)	6 (85.7%)
Year 1	6	2 (33.3%)	0	4 (66.7%)	0	6 (100%)
Year 3	8	2 (25%)	1 (12.5%)	5 (62.5%)	0	8 (100%)
Year 5	7	1 (14.3%)	0	6 (85.7%)	0	7 (100%)
Year 10	5	1 (20%)	0	4 (80%)	0	5 (100%)
Year 15	6	0	0	6 (100%)	0	6 (100%)
Year 20	5	0	0	5 (100%)	0	5 (100%)

Table 3. Visual acuity readings at standardised follow-up points. (N: number; NPL: no perception of light) (no robust statistical analysis could be performed due to the small number of patients and variability in follow-up).

t	N eyes	Median (range)	logMAR >0.3	logMAR >1.0
Baseline	11	0 (−0.5; 0.7)	111 (9.1%)	011
Year 1	12	0.04 (−0.08; 0.7)	112 (8.3%)	012
Year 3	16	0.05 (−0.23; 1)	116 (6.3%)	116 (6.3%)
Year 5	14	0.19 (0; 1.5)	414 (28.6%)	114 (7%)
Year 10	10	0.2 (0; 1)	410 (40%)	210 (20%)
Year 15	12	0.3 (0; NPL)	812 (66.7%)	212 (16.7%)
Year 20	10	0.7 (0.1; NPL)	810 (80%)	310 (30%)

Treatment and disease control

At baseline, ocular inflammation developed in 6 of 7 patients while they were receiving systemic treatment for arthritis, including methotrexate (5 of 6 patients), adalimumab (1 of 6 patients), etanercept (2 of 6 patients), and infliximab (1 of 6 patients) (See Table 4). At 1-year follow-up, 5 of 6 patients were treated with a biologic anti-TNF agent (adalimumab in 4 and etanercept in 1), and 1 or more immunomodulating therapy (IMT) (mycophenolate mofetil [MMF] and/or methotrexate [MTX]). One patient was on oral glucocorticosteroids and anti-tubercular treatment initially for suspected ocular tuberculosis, which was later proven to be Blau syndrome.

At year 5, 10, 15 and 20, all patients were receiving multiple systemic drugs, including a biologic agent, oral corticosteroids, and one or more IMT (triple or quadruple therapy). Most patients were administered topical steroid eye drops (prednisolone acetate 1%): 83.3%, 87.5%, 92.9%, 80%, 83.3%, and 70% of involved eyes at year 1, 3, 5, 10, 15, and 20 of follow-up. The percentage of involved eyes with AC cells ≥1 was 57.1%, 58.3%, 31.3%, 71.4%, 60%, 41.7%, and 30% at year 1, 3, 5, 10, 15 and 20, respectively. Disease control, defined as having <1+ cells in both eyes and using topical steroid eye drops less than twice daily, was achieved in 2 out of 6 patients (33.3%) at year 1, in 3 of 8 patients (37.5%) at year 3, in 1 in 7 patients (14.3%) at year 5, in 1 in 5 patients (20%) at year 10, in none of the 6 patients at year 15 and 1 in 5 patients (20%) at year 20. Systemic treatment was guided by ocular inflammation in all patients, with joint symptoms flaring only during episodes of active uveitis.

Complications and ocular surgery

Structural ocular complications are presented in Table 5. It should be noted that many patients with longstanding disease had limited fundal view due to synechiae and media opacities. Consequently, OCT of macula and discs was heavily relied upon for fundus assessment in these patients. Optic disc swelling was observed in a range of 35.7–66.7% of patients at any

Table 4. Overview of medical treatment throughout follow-up (Pred = Prednisolone; MTX = Methotrexate; ADA = Adalimumab; IFX = Infliximab; ETA = Etanercept; ABA = Abatacept; TCR = Tacrolimus; MMF = Mofetil Mycophenolate; RTX = Rituximab; TOC = Tocilizumab; GOL = Golimumab; IVMP = Intravenous Methylprednisolone).

	Baseline	Year 1	Year 3	Year 5	Year 10	Year 15	Year 20
1	Pred, MTX, ADA	Pred, MTX, ADA	Pred, MTX, ADA				
2	MTX, IFX	Pred, MTX, TCR, ADA	Pred, MTX, TCR, ABA	Pred, TCR, IFX			
3	ETA	Pred, ETA	Pred, MMF	Pred, MMF, RTX	Pred (pregnant)	Pred, TOC	
4	Pred, MTX	Pred, MMF, ADA	Pred, MTX, MMF, IFX	Pred, MMF, IFX			
5							
6			MTX, ADA	MTX, IFX			
7						Pred, MMF	Pred, MMF, ADA
8	Pred, MTX	MTX, MMF, ADA	MTX, MMF, ADA	IVMP, MTX, MMF, IFX	Pred, MTX, MMF, IFX+IVMP		
9			Pred, MTX, IFX	Pred, MMF, IFX	Pred, MMF, IFX	Pred, MMF, IFX	Pred, MMF, IFX
10						Pred, MTX, MMF, IFX	Pred, MMF, IFX
11	MTX, ETA	Pred[a]	MTX, IFX	Pred, MTX, IFX	Pred, MTX, IFX		
12					Pred, MTX, IFX	Pred, MTX, MMF, ADA	Pred, MMF, GOL
13						Pred, MTX, ADA	Pred, MTX, ADA

[a]Additionally on antitubercular treatment due to suspected ocular tuberculosis.

Table 5. Prevalence of structural ocular complications (N: Number of eyes; BKP: Band Keratopathy; OHT: Ocular Hypertension; CMO: Cystoid Macular Oedema; CNV: Choroidal Neovascular Membrane). Of note: optic disc swelling and CMO were assessed via optical coherence tomography (OCT) imaging and can be considered both a structural complication and an indicator of posterior inflammation.

t	N	BKP	Cataract	Optic disc swelling	Disc pallor	OHT glaucoma	Hypotony	CMO	CNV
Baseline	14	0 (0%)	0 (0%)	5 (35.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Year 1	12	0 (0%)	1 (8.3%)	6 (50%)	0 (0%)	2 (16.7%)	0 (0%)	0 (0%)	0 (0%)
Year 3	16	0 (0%)	2 (12.5%)	11 (68.8%)	0 (0%)	2 (12.5%)	0 (0%)	0 (0%)	0 (0%)
Year 5	14	0 (0%)	4 (28.6%)	10 (71.4%)	0 (0%)	4 (28.6%)	0 (0%)	3 (21.4%)	0 (0%)
Year 10	10	2 (20%)	6 (60%)	4 (40%)	4 (40%)	0 (0%)	0 (0%)	3 (30%)	0 (0%)
Year 15	12[a]	612 (50%)	10 (83.3%)	411 (36.4%)	411 (36.4%)	311 (27.3%)	312 (25%)	311 (27.3%)	211 (18.2%)
Year 20	10[a]	610 (60%)	8 (80%)	69 (66.7%)	29 (22.2%)	39 (33.3%)	39 (33.3%)	59 (55.6%)	29 (22.2%)

[a]Right eye of patient 7 phthisical, with no fundal view.

timepoint through follow-up, including baseline, whereas CMO was only detected after 5 years (range 21.4%–55.6%) (see Table 5). Eight patients (12 eyes) developed visually significant cataracts and underwent cataract surgery (with IOL implantation in 10 of 12 eyes [83.3%]), after a median disease duration of 7 years (range 5–17 years). Two patients (2 eyes) had acute angle closure glaucoma (treated with iridectomy), after 6 and 9 years, respectively. Three patients required filtering surgery due to uncontrolled glaucoma: trabeculectomy was performed in 2 eyes, and Ahmed valve surgery in one eye. Following surgery, intraocular pressure was effectively controlled, although antiglaucoma drops were still necessary in all eyes. Five patients required vitreoretinal surgery during follow-up. One patient (one eye) underwent a vitrectomy with SF6 tamponade due to hypotony following insertion of a steroid implant (intravitreal dexamethasone implant, Ozurdex®). Four other patients (4 eyes) developed retinal detachment, all of which required vitrectomy with oil tamponade and additional scleral buckling in 1 case. Silicone oil was subsequently removed in 2 of 4 eyes. Rhegmatogenous retinal detachment developed in two phakic and one pseudophakic eye (5 years following cataract surgery), and a tractional detachment was detected in an aphakic eye 18 years after cataract surgery. Overall, detachments occurred at year 6, 9, 10 and 18 of follow-up." At the last follow-up, the retina was successfully attached in 3 out of 4 eyes.

Discussion

This study presents long-term outcomes of ocular involvement in patients with Blau syndrome, and highlights the significant, progressive visual morbidity in this monogenic autoinflammatory condition. Despite intense immunosuppressive treatments, including biologics, most patients experienced persistent uveitis activity, with only 15–35% achieving disease control at each time point. The cumulative damage due to chronic disease activity and administered treatments resulted in unfavourable visual outcomes, including progressive visual acuity loss. Structural complications were common, with approximately 50% of patients undergoing cataract surgery around 7 years after first diagnosis of uveitis. Uncontrolled glaucoma and retinal detachment were also frequently detected, which required surgical intervention in 20% and 15% of eyes, respectively.

As seen in this cohort, the disease typically manifests with cutaneous and articular symptoms initially, followed by ocular manifestations.[1] Of note, corneal subepithelial opacities were detected in two patients during ocular screening for suspected JIA at onset of arthritis, whereas uveitis developed years later. Nummular corneal opacities have been reported in several patients with Blau syndrome, but not as an isolated ocular finding preceding uveitis.[10–12] More than half of patients (57%) initially presented with anterior uveitis, but all patients in this series eventually developed panuveitis later in the disease course. This trend expands on a prior report on 38 patients with (partial) 3-year follow-up data, in which duration of eye disease was significantly correlated with the presence of panuveitis.[6]

Currently, children with Blau syndrome and uveitis are mostly treated similarly to those with JIA, using corticosteroids, methotrexate, and biologic agents. Early introduction of biologic agents has been emphasized to prevent major visual impairment/blindness in Blau syndrome.[13,14] Among these biologic agent, TNF-α inhibitors, particularly infliximab, are the most widely used biological therapy in this disorder.[15] Targeting TNF-α in Blau syndrome has a molecular rationale, as pre-exposure to TNF-α or functionally similar cytokines during macrophage development is vital for NF-κB-driven proinflammatory signalling and accelerated inflammatory responses upon IFN-γ stimulation in Blau syndrome.[16] The only patient with monocular blindness (no light perception due to phthisis) in this cohort had the longest delay in introducing biologics (15 years after the first episode of uveitis). Complete visual loss was also detected in 7 of 38 patients with Blau syndrome-associated uveitis in a cohort from Japan[7] and 5 of 8 patients in a Chinese series,[17] all of whom had not been treated with biologics from a young age, mostly due to diagnostic delay. Although biologics usually do not offer sufficient disease control to wean patients off oral corticosteroids, they may help prevent complete visual loss in patients with Blau syndrome-associated uveitis due to their more targeted approach. Prospective, large-scale trials are needed to determine the optimal therapeutic approach in Blau syndrome-associated uveitis, including non-TNF-α biologics and janus kinase inhibitors.

While this report has limitations in terms of small sample size, its retrospective design and the variable follow-up of patients, it does highlight the significant visual morbidity in patients with longstanding Blau syndrome-associated uveitis. There is an unmet need for an evidence-based therapeutic approach in this rare, potentially blinding condition.

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