BMC Pediatrics

RESEARCH

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Long-term prognosis of 47 pediatric patients with Blau syndrome in China

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Abstract

Objectives Blau syndrome (BS) is a rare autoinflammatory disease characterized by a clinical triad of uveitis, dermatitis and arthritis. The aim of our study was to summarize organ involvement, predict disease prognosis and evaluate treatment response.

Methods Clinical data of 47 Chinese children who were diagnosed with Blau syndrome in Beijing Children's hospital, Capital Medical University was retrospectively analyzed. Direct sequencing of NOD2 gene was performed by sanger sequencing. Data were analyzed through SPSS 21.0. A Bayesian network was constructed to integrate prediction algorithms of genetic mutations and clinical manifestations, exploring the complex relationship between genotype and phenotype through R (Version 4.4.1, R Core Development Team). P value < 0.05 was significant.

Results The 47 patients included 26 males and 21 females. Median age of disease onset was 13.64 months, ranging from 1 to 51 months. At baseline, incidence of fever, arthritis, rash, dermatitis and uveitis were 34%, 93.6%, 72.3% and 31.9%. Nearly 30% patients (14 patients) presented with characteristic triad. Incidence of vasculitis and interstitial lung disease were 27.7% and 17.0%, respectively. Inflammatory indices (e.g., erythrocyte sedimentation rate and C reactive protein) were above normal range. Twelve different NOD2 mutations were identified. R334Q was associated with arthritis, rash, uveitis and fever, whereas R334W was associated with arthritis, rash and fever. Approximately 95.7% patients (45 patients) were treated with combination of prednisolone and methotrexate and 42.6% patients (20 patients) were treated with tumor necrosis factor inhibitors. At the most recent follow-up visit, 34 patients (72.3%) achieved disease control. Patients treated with TNF-α inhibitors had a higher remission rate.

Conclusions Clinical manifestations of Blau syndrome in this study were various. TNF-α inhibitors were effective in inducing remission rate of Blau syndrome.

Keywords Blau syndrome, Granulomatous arthritis, Granulomatous dermatitis, Granulomatous uveitis, TNF-α inhibitors

Introduction

Blau syndrome (BS) is a rare granulomatous autoinflammatory disease with onset typically occurring before the age of four years. First reported by Edward Blau in 1985, the disease was identified as an autosomal dominant trait through analysis of 11 family members across four generations [1]. In the same year, Douglas Jabs reported a similar family of 3 generations [2]. In 2001, mutations in the NOD2 gene, located on chromosome 16, were identified as the genetic basis of BS [3]. The NOD2 gene

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encodes nucleotide oligomerization domain 2, an intracellular pattern-recognition receptor that regulates host immunity. Mutation of NOD2 gene leads to activation of NF-kB pathway and cause chaos in host immune system [4]. Blau syndrome is characterized by a clinical triad of granulomatous dermatitis, arthritis and uveitis. Dermatitis usually occurs before four years of age as initial symptoms. Scaly erythematous plaques (SE) and lichenoid papules (LP) are common skin lesions. Arthritis is symmetrical and boggy which can progress to camptodactyly and restricted movement. Uveitis, associated with high mortality, presents as granulomatous panuveitis [4]. Although rare, involvement of other organs (e.g., liver, kidney, lung, cardiovascular system, and central nervous system) has been reported.

Diagnosis of BS is based on pediatric onset of clinical triad, histopathological finding of non-caseating granulomas in skin, synovia or other affected tissues [4]. Genetic mutation of NOD2 gene could confirm the diagnosis. Due to the rarity of BS, no therapeutic guidelines are available. Main treatment goal is to prevent the progression of arthritis and uveitis. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used on-demand for pain relief. High doses of glucocorticoids are used during active disease, while low doses are used during quiescent phase. Immunosuppressive agent like methotrexate and thalidomide were effective in refractory patients. Biologics (e.g., tumor-necrosis factor- α inhibitors, IL-1 and IL-6 receptor antagonists) had yield satisfactory response in Blau syndrome.

Several cohort study of Blau syndrome published in recent years [5–7]. Other studies about Blau syndrome are most case series [8, 9]. However, data about Blau syndrome in Chinses populations are scarce. This article focuses on the clinical characteristics, treatment options, and long-term prognosis of patients at a tertiary care center in China.

Method

Study population

The retrospective study involved 47 pediatric patients in Beijing Children's Hospital, Capital Medical University from 16th June 2006 to 30th June 2023. All patients were under 18 years of age. Patients were included if they met the classical triad criteria or had a confirmed Blau syndrome diagnosis with a NOD2 gene mutation (pathogenic and likely pathogenic according to ACMG classification [10]) or pathological examination showing non-caseating granuloma with multinuclear cells. Patients with other rheumatic diseases were excluded. Clinical information on disease onset, clinical manifestation, laboratory test, treatment and prognosis were collected from the database.

Ethical statement

Written informed consent was obtained from patient and their parent. This study gained approval from the Ethics Committee of a hospital on 16 June 2022 ([2022]-E-134-R).

Data collection

Genomic DNA was extracted from peripheral blood and whole genome sequencing was performed. Sequencing of exons and introns of NOD2 gene was confirmed by sanger sequencing. Biopsies of skin and affected joints were conducted and pathological examinations were performed. Intermittent fever was defined as elevated temperature followed by an interval of normal temperature. Persistent fever was fever that last more than 2 weeks. Oligoarticular joint involvement was defined as less than 5 affected joints whereas polyarticular involvement was defined as five or more affected joints. Disease activity was assessed through inflammatory indices and clinical manifestations. At each follow-up visit, inflammatory indices and radiology images were applied.Disease control, defined as patients without Blau syndrome-associated clinical manifestations and had normal level of inflammatory indices.

Statistical analysis

Data was analyzed using SPSS 21.0 and R (Version 4.4.1, R Core Development Team). Baseline and follow-up data were analyzed through Wilcoxon single rank test and Paired t-test. Data were presented as number (%), median [IQR], or mean ± SD. $P < 0.05$ was significant. In order to delve deeper into the correlation between genetic mutations and clinical manifestations, we developed a Bayesian network. This network serves as a visual representation that captures the probabilistic interconnections between variables of interest. Consider $X = \{x_1, x_2, \ldots, x_n\}$ as a collection of such variables. A Bayesian network, constructed over this set, is characterized by a network structure S, which is essentially a directed acyclic graph (DAG) encompassing *X*, along with a set *P* of local probability distributions. This structure *S* embodies the principle of conditional independence, meaning that each variable xi is conditionally independent of its non-descendants when its parents in S are known. For the purposes of this study, the nodes within our Bayesian network encompass both genetic mutations and clinical manifestations. The conditional probabilities of these variables, given their parental nodes, are depicted within the Bayesian network through Gaussian conditional densities. Operating under the premise of parameter

independence, we initially derived the Bayesian network structure S from our training dataset. Subsequently, employing a greedy search algorithm with random restarts, we navigated towards the network with the highest posterior score, effectively circumventing local maxima. Ultimately, we refined our Bayesian network through a heuristic search within the defined network space, aiming to maximize the Bayesian factor, thereby achieving an optimized model. Construction of Bayesian networks were done using BNarray package of R software (http://www.r-project.org).

Results

Of 47 patients assessed, 26 (55.3%) were male and 21 (44.7%) were female. All patients were Han Chinese. Eight cases (17.0%) came from seven unrelated families and 39 cases (83%) were sporadic. Median age of disease onset was 13.64 ± 2.00 months (range from 1 to 51 months). Nearly 60% of patients had disease onset before one year of age. Median age of disease diagnosis was 54.87 ± 5.66 months. Median time lag from disease onset to diagnosis was 41.23 ± 5.10 months. General information and organ involvement at first prescription are shown on Table 1. At disease onset, five patients (10.6%) presented with single system involvement, while others presented with multisystem involvements.

Fever

Sixteen patients (34%) had fever in early stage of disease course (Fig. 1A), including 2 patients (4.3%) had intermittent fever and 14 patients (29.8%) with persistent fever. Among them, 3 patients (6.4%) had R334Q mutation, 2 patients (4.3%) had R334W, R587C and M513T mutations. One patient (2.1%) had R471C, C495Y and G481D mutations.

Joint involvement

Arthritis was the most common symptoms which involved 44 patients (93.4%). Thirty-four (77.3%) patients had polyarthritis and 10 (21.3%) patients had oligoarthritis. Arthritis was boggy (41 patients, 93.2%), symmetrical (Fig. 2A) and mainly involving ankles (40 patients, 90.9%), wrists (32 patients, 72.3%) and knees (31patients, 70.2%). Small joints (e.g., proximal interphalangeal joint and metatarsal-phalangeal joint) were also involved. One patient (2.1%) had camptodactyly. In nine cases (19.1%), arthritis preceded skin lesions. In other cases, onset of arthritis was later than skin lesion but earlier than ocular manifestations (Fig. 1 B-D).

Skin lesions

Thirty-four (72.3%) patients had skin lesions which mainly manifested as scaly papules and lichenoid-like rash (Fig. 2B). Dermatitis was usually the first complain of BS patients, symmetrically distributed on trunk and extremities.

Ocular involvement

Fifteen patients had ocular involvement, among them, 13 were bilateral and 2 were unilateral. Onset of ocular involvement was at nearly 34 months. Common signs of ocular involvement in Blau syndrome were uveitis, ocular pain, photophobia and blurred vision. Twelve patients (23 eyes) had uveitis (Fig. 2C). Among them, four patients (eight eyes) had granulomatous uveitis as evidenced by the presence of mutton-fat keratic precipitates. Ocular pain and photophobia were found in 10 eyes (5 patients), corneal nebula in 8 eyes (4 patients), blurred vision in 8 eyes (4 patients), glaucoma in one eye (1 patient), and anisocoria in one patient. No patients were blind at baseline.

Other system involvement

Incidence of vasculitis and interstitial lung disease were 27.66% (13/47) and 17.0% (8/47). Abdominal aorta (5 cases, 10.6%), common carotid artery (5 cases, 10.6%) and renal artery (4 cases, 8.5%) were more commonly involved. To summarize, medium and large-sized vessel were predominantly involved. In our study, hypertension was found in 4 patients (8.5%), two of whom had severe renal artery stenosis. Regarding cardiac involvement, 3 patients (6.4%) presented with increased diameter of left ventricle. Three patients (6.4%) had deafness and two patients (4.3%) had microscopic hematuria. Osteochondroma in interphalangeal joint was noted in one patient (2.1%). Demyelinating lesions under MRI were found in one patient (2.1%) without neurological or psychiatric symptoms.

Laboratory test

Routine blood tests, including blood cells, platelets, kinases, creatinine and urea nitrogen were normal. Inflammatory indices like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) at baseline were above normal range (Table 2). Thirty-four patients (72.3%) performed fine-needle aspiration of affected skin and synovia, with non-caseating granulomas were found in 26 cases (76.5%).

NOD2 genetic variants

All patients in our study completed genetic analysis of NOD2 gene. Twelve different genetic variants were

Table 1 General information and organ involvement at first inintiation

Patient no	Sex	Family history	Genotype	Age at onset (months)	Age at presentation (months)	Delay in diagonosis from onset(months)	Articular involvement	Rash	Uveitis	Other manifestations	Duration of follow-up (months)
1	M	No	c.1538 T > C(M513T) Classfication:Likely pathogenic	2	44	42	Polyarthritis(wrist, ankle and small joints of hands); Boggy swelling; Tenosynovitis	papule	Bilateral corneal nebula; Bilateral granulomatous uveitis	Nerve deafness	143
2	M	No	c.1759C > T(R587C) Classfication:Likely pathogenic	36	142	106	Polyarthritis(wrist, knees and ankle)	pigmentary macula	Uilateral glaucoma	Fever	1
3	F	No	c.1484G > A(C495Y) Classfication:Likely pathogenic	27	36	9	Polyarthritis(wrist, knees, ankle and small joints of hands)			Fever	136
4	M	Yes, affected father	c.1001G > A(R334Q) Classfication: Pathogenic	5	60	55	Polyarthritis(wrist, elbows, knees and ankle); Boggy swelling	Papule	Bilateral corneal nebula; Anisocoria; Bilateral granulomatous uveitis	Artertis; Interstitial lung disease; Cardiac involvement; Nerve deafness	96
5	M	No	c.1001G > A(R334Q) Classfication: Pathogenic	4	28	24	Polyarthritis(wrist, ankle and small joints of hands); Joint deformities; Boggy swelling	papule			11
6	M	No	c.1000C > T(R334W) Classfication: Pathogenic	2	69	67					2
7	M	No	c.1148A > G(E383G) Classfication:Likely pathogenic	12	158	146	Polyarthritis(wrist, knees and ankle); Boggy swelling				74
8	M	No	c.1759C > T(R587C) Classfication:Likely pathogenic	24	43	19	Oligoarthritis(knees and ankle); Boggy swelling			Fever	107
9	M	No	c.1534G > T(D512Y) Classfication:Not classified	18	46	28	Oligoarthritis(knees and ankle);	papule	Bilateral corneal nebula; Optic disc edema	Artertis	131
10	F	No		13	67	54	Polyarthritis(small joints of hands, wrist, elbows, knees and ankle); Boggy swelling	papule		Artertis; Interstitial lung disease; Renal involvement	77

Table 1 (continued)

Patient no	Sex	Family history	Genotype	Age at onset (months)	Age at presentation (months)	Delay in diagonosis from onset(months)	Articular involvement	Rash	Uveitis	Other manifestations	Duration of follow-up (months)
11	F	No		3	44	41	Oligoarthritis(wrists and ankle); Boggy swelling;	papule	Uilateral uveitis(right)	Artertis; Cardiac involvement; Hypertension	75
12	M	Yes, affercted mother and grand-mother	c.802C > T(P268S) Classfication:Likely benign	30	38	8	Polyarthritis(small joints of hands, wrist, and ankle); Boggy swelling	papule			27
13	M	No		42	45	3	Polyarthritis(knees, small joints of hands and feet, shoulders, hips, and ankle); Boggy swelling	papule		Fever; Interstitial lung disease	126
14	F	Yes, affected twins older sister	c.1000C > T(R334W) Classfication: Patho-genic	12	50	38	Polyarthritis(knees, elbows, and ankle); Boggy swelling	papule		Fever	31
15	F	Yes, affected twins younger sister	c.1000C > T(R334W) Classfication: Patho-genic	1	45	44	Oligoarthritis(knees, ankle and elbows); Boggy swelling;	papule		Artertis; Interstitial lung disease; Hyper-tension	16
16	F	No	c.1001G > A(R334Q) Classfication: Patho-genic	3	13	10	Polyarthritis(knees, small joints of hands, wrists and ankle); Boggy swelling	papule		Fever; Artertis; Hypertension	99
17	M	No		18	34	16	Polyarthritis(wrists, ankle and knees); Boggy swelling; Joint deformities	papule	Bilateral uveitis	Artertis	5
18	F	Yes, affected grand-mother, aunt and father	c.1000C > T(R334W) Classfication: Patho-genic	9	22	13	Polyarthritis(wrists, ankle and knees); Boggy swelling;	papule		Artertis	107
19	F	No	c.1759C > T(R587C) Classfication:Likely pathogenic	8	40	32	Oligoarthritis(wrists, ankle and knees); Boggy swelling;				31
20	M	No	c.1411C > T(R471C) Classfication:Likely benign	8	60	52	Polyarthritis(wrists, ankle, knees and small joints of hands); Boggy swelling;	papule		Fever; Cardiac involvement; Hypertension; Osteochon-droma	31

Table 1 (continued)

Patient no	Sex	Family history	Genotype	Age at onset (months)	Age at presentation (months)	Delay in diagonosis from onset(months)	Articular involvement	Rash	Uveitis	Other manifestations	Duration of follow-up (months)
21	F	No	c.1001G > A(R334Q) Classfication: Pathogenic	9	71	62	Polyarthritis(wrists, ankle and small joints of hands); Boggy swelling; Joint deformities	papule		Fever; Artertis	8
22	M	Yes, affercted mother	c.1484G > A(C495Y) Classfication:Likely pathogenic	1	85	84	Polyarthritis(wrists, ankle, knees, elbows and small joints of hands); Boggy swelling; Joint deformities	papule			64
23	M	No	c.1442G > A(G481D) Classfication:Likely pathogenic	1	44	43	Polyarthritis(ankle, knees and small joints of hands)	papule		Fever	1
24	F	No	c.1538 T > C(M513T) Classfication:Likely pathogenic	12	23	11	Polyarthritis(wrists, ankle, knees and small joints of hands); Boggy swelling; Joint deformities			Fever	60
25	M	No	c.1761 T > G(R587R) Classfication:Likely benign	1	24	23	Polyarthritis(wrists, knees, ankle and small joints of hands); Boggy swelling;				1
26	M	No	c.1001G > A(R334Q) Classfication: Pathogenic	13	44	31	Polyarthritis(wrists, elbows, knees, ankle and small joints of hands); Boggy swelling;		Bilateral granulomatous uveitis; Bilateral corneal nebula		89
27	M	No		11	45	34	Polyarthritis(wrists, ankle and knees); Boggy swelling;				1
28	F	No	c.1001G > A(R334Q) Classfication: Pathogenic	2	83	81	Polyarthritis(wrists, elbows, knees, ankle and small joints of hands); Boggy swelling; Joint deformities	papule	Bilateral granulomatous uveitis	Fever; Artertis; Renal involvement	2

Table 1 (continued)

Patient no	Sex	Family history	Genotype	Age at onset (months)	Age at presentation (months)	Delay in diagonosis from onset(months)	Articular involvement	Rash	Uveitis	Other manifestations	Duration of follow-up (months)
29	F	No		12	36	24	Oligoarthritis(ankle and knees); Boggy swelling;	papule			70
30	M	Yes, affercted mother		36	84	48	Polyarthritis(wrists, elbows, shoulders, ankle and small joints of hands); Boggy swelling;	papule	Bilateral blurred vision; Bilateral uveitis	Fever	1
31	F	Yes, affercted mother	c.1000C > T(R334W) Classfication: Pathogenic	7	12	5	Polyarthritis(wrists, elbows, knees, ankle and small joints of hands and feet); Boggy swelling;	papule		Artertis	82
32	F	No		3	23	20	Polyarthritis(wrists, and small joints of hands and feet); Boggy swelling;			Interstitial lung disease	6
33	F	No		7	38	31	Polyarthritis(wrists, knees and ankle); Boggy swelling;	papule			45
34	F	No		22	92	70	Oligoarthritis(wrists and knees); Boggy swelling; camptodactyly	lichenoid-like rash	Bilateral uveitis; Bilateral blurred vision		22
35	F	No	c.1000C > T(R334W) Classfication: Pathogenic	9	45	36	Polyarthritis(ankle, wrist, small joints of hands and feet, elbows and knees); Boggy swelling; Joint deformities		Bilateral blurred vision; Bilateral uveitis	Fever	27
36	M	No	c.1538 T > C(M513T) Classfication:Likely pathogenic	12	16	4	Polyarthritis(ankle, knees,wrist, elbows, small joints of hands and feet); Boggy swelling; Joint deformities	lichenoid-like rash		Fever; Interstitial lung disease; Central nervous system involvememt	34
37	M	No		4	34	30	Oligoarthritis(ankles and knees); Boggy swelling;				1

Table 1 (continued)

Patient no	Sex	Family history	Genotype	Age at onset (months)	Age at presentation (months)	Delay in diagonosis from onset(months)	Articular involvement	Rash	Uveitis	Other manifestations	Duration of follow-up (months)
38	M	No	c.1538 T > C(M513T) Classfication:Likely pathogenic	22	25	3	Polyarthritis(wrist, knees,ankle and small joints of hands); Boggy swelling; Joint deformities	papules		Interstitial lung disease	2
39	M	No		51	87	36	Oligoarthritis(ankle); Boggy swelling;			Artertis	23
40	F	No		22	82	60	Oligoarthritis(ankle, wrist); Boggy swelling;	papules	Bilateral uveitis		1
41	F	No	c.1426A > C(T476P) Classfication:Likely pathogenic	34	106	72	Polyarthritis(ankle, knees and wrist); Boggy swelling;	papules	Bilateral uveitis		1
42	M	No		4	7	3		papules		Fever; Interstitial lung disease	1
43	M	No		56	160	104	Polyarthritis(ankle, small joints of hands, knees, wrist and hips); Boggy swelling; Joint deformities	papules		Fever	1
44	M	No		3	13	10	Polyarthritis(ankle, small joints of hands and feet); Boggy swelling;	papules	Photophobia; Bilateral uveitis		4
45	F	No		4	21	17	Polyarthritis(ankle, wrist, small joints of hands and feet); Boggy swelling;	papules			1
46	M	No		4	160	156	Polyarthritis(ankle, wrist, small joints of feet and elbows); Boggy swelling;	papules	Bilateral blurred vision		1
47	M	No		2	35	33	Polyarthritis(knees, ankle, small joints of hands and feet); Boggy swelling;	papules		Artertis; Nerve deafness	8

identified in 28 patients. P.R334W and p.R334Q variants were the most abundant and were found in 12 patients (5 familial and 7 sporadic cases). Six patients had p.R334W variants (4 familial and 2 sporadic cases), six patients had p.R334Q variants (1 familial and 5 sporadic cases), 4 patients had p.M513T variants (all sporadic cases), 3 patients had p.R587C variants (all sporadic cases), 2 patients had p.C495Y variants (1 familial and 1 sporadic cases). The p.E383G, p.G481D, p.P268S, p.R471C, p.T476P, p.R587R and p.D512Y variants were found in one sporadic case.

Genotype–phenotype relationship

After applying logistic regression by SPSS, no strong relationship was found between the two most frequent mutations (p.R334W and p.R334Q) and phenotype. Further, a Bayesian network was constructed using R. We found that R334Q is associated with arthritis, rash, uveitis and fever, whereas R334W is associated with arthritis, rash and fever (Fig. 3).

Treatment

In our study, four types of drugs were used including NSAIDs, corticosteroids (prednisolone), immunosuppressant agent (methotrexate, leflunomide, cyclosporine and thalidomide) and biologics (TNF-α inhibitors). Oral prednisolone and methotrexate usually used as first line treatment. In our study, 45 patients (95.7%) used a combination of prednisolone and methotrexate, one patient (2.1%) used prednisolone combined with another immunosuppressant agent and all patients used NSAIDs as pain relieving agents. Cyclosporin was used in 4 patients (8.5%), thalidomide in 5 cases (10.6%), leflunomide in 2 cases (4.3%).

Biologics

Antitumor necrosis factor agents were used to treat 34 patients (72.3%). Tumor necrosis factor (TNF)-α inhibitors used in our study were mainly adalimumab, infliximab and etanercept. Indication of starting biologics were severe or aggravated skin lesions, arthritis, ocular manifestation and other system involvement. Disease course before TNF-α inhibitors initiation and the duration of TNF-α inhibitors treatment were 6.53 ± 2.74 months and 42.68 ± 6.03 months. Before using TNF-α inhibitors, 16 patients (34.0%) had intermittent fever, 33 patients (70.2%) had skin lesions, 34 patients (72.3%) had active arthritis and 21 (61.8%) patients had active ocular disease. Inflammatory indices like CRP and ESR were elevated (Table 3). Due to high disease activity, prednisone and methotrexate were administered prior to TNF inhibitors.

Prognosis

At the last follow-up visit, median age of patient was 94.53 ± 7.95 months (range from 8–232 months) and time of follow-up visit was 40.06 ± 6.52 months (range from 1–143 months). Disease activity improved after treatment in multiple aspects. Clinical manifestation improved markedly. All patients with fever had their body temperature normalized. Arthritis was controlled in 39 patients (88.6%), and a 30% response rate was achieved in 43 patients (97.7%). Skin lesions resolved in 29 patients (85.3%), with a 30% response rate of 100%. Uveitis was resolved in 9 patients (60%), while six patients (40%) still had active ocular manifestations. Under regularly radiological assessment of vascular involvement, 10 patients reached 30% response rate and 8 patients showed no lesions under contract enhance CT. In terms of inflammatory indices, serum level of C-reactive protein, erythrocyte sedimentation rate, ferritin and serum amyloid A protein decreased significantly (Table 2). At baseline, eight patients (17.0%) had elevated procalcitonin levels, which did not significantly improve during follow-up visits. As for downgrade medication, the median dosage of steroids was taped to 0.087 ± 0.05 mg/kg (range from 0–1.71 mg/kg, $P < 0.001$).

During follow-up visits, 34 patients (72.3%) reached disease control. Among patients who follow-up for one year, 79.1% achieved disease control. Among patients follow-up for 5 years, 72.4% achieved disease control. Among those follow-up for 10 years, 62.5% achieved disease control. The average time to reach disease control was 34.6±6.2 months. Average duration of disease control was 16.5±3.0 months. No significant difference was observed in disease control between the two most frequent mutations, p.R334W and p.R334Q.

Among patients treated with TNF-α inhibitors, clinical manifestation like skin, articular and ocular involvement improved. Serum level of CRP, ESR, SF, SAA and PCT decreased significantly (Table 3). Daily dose of prednisolone significantly decreased to 0.71 ± 0.07 mg/kg (range from 0–1.67 mg/kg, $P < 0.001$). Thirty-two patients reached disease control remission state. In contrast, only two patients treated with combination of NSAIDs and DMARDs reached disease control. Compared with patients treated with non-biologics, biologics treatment increased the rate of disease control.

Discussion

Blau syndrome is an autosomal dominant disease caused by mutation of NOD2 gene. Previous studies found that mutation of NOD2 gene cause auto-activation of NF-κB pathway, release lots of pro-inflammatory cytokines and cause tissue damage [4]. The aim of our study was to

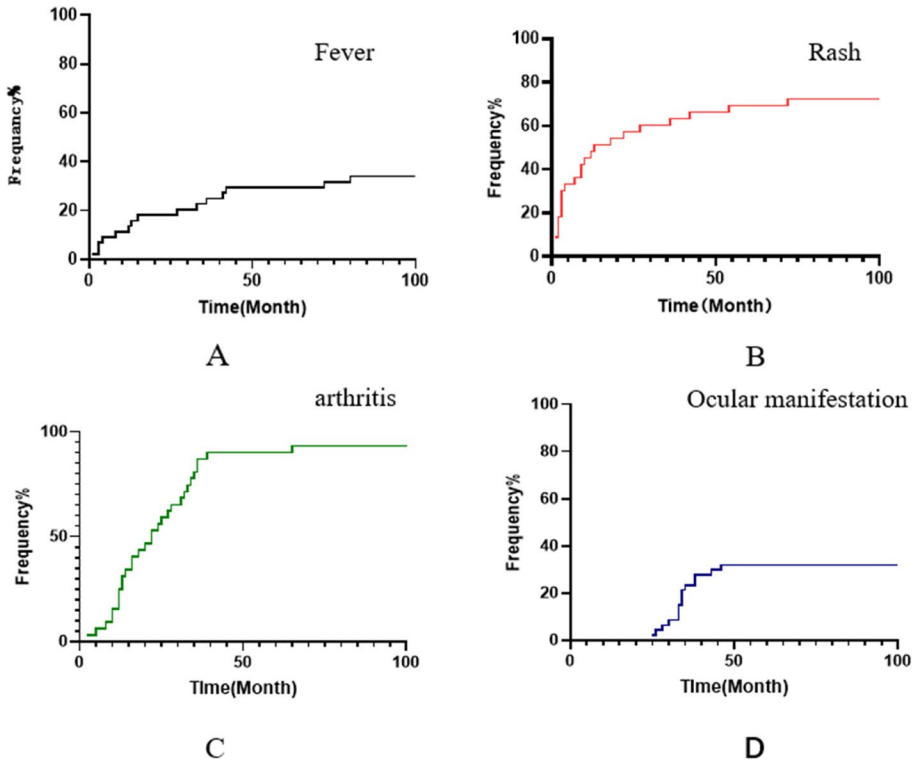

Fig. 1 Frequency and patient's age of fever and clinical triad of Blau syndrome. **A** Fever. **B** Rash **C** Arthritis **D** Ocular manifestation

summarize clinical characteristics and evaluate efficacy of different treatment options.

Rash, arthritis and uveitis are clinical triad of Blau syndrome. Rash usually appears at first year of life, followed by arthritis which appears at 2 to 4 years of age and uveitis appears at nearly four years of age [11]. The incidence of fever, skin rash, arthritis and eyes involvement in our study were 34%, 72.3%, 93.6% and 31.9%. Fever, although not included in the typical triad, is an important clinical manifestation in pediatric Blau syndrome [12]. Our results are in accordance with a study in Japan, whereas 52% of patients had fever, 91% had skin rash, 91% had arthritis and 36% had eye involvement [6]. About 1/3 to 1/2 patients presented with ex-triad symptoms. Vasculitis, once a rare manifestation in Blau syndrome, has been increasingly reported in recent years, with all sizes of vessels being affected. In our study, 27.66% of patients presented with BS associated arthritis. Large and medium sized arteries were the most commonly involved. Eighteen cases of Blau syndrome associated arthritis were identified through literature review, with 14 having aortoarteritis and four having renal artery involvement [13]. Recent studies found that NOD2 induce overexpression of cytokines in affected vessels and promote disease progression [14]. In-depth research should place a focus on the mechanism of Blau syndrome associated vasculitis. Our study also reported a case of osteochondroma in the interphalangeal joint, which had never been previously reported and carried the p.R471C mutation.

In 2001, Miceli-Richard et al. firstly found susceptibility gene for Blau syndrome-NOD2 gene and 3 missense genetic variants (R334Q, R334W and L469F) [15]. Until now, over hundreds of genetic variants were discovered, most of which are located in NATCH and LRR region. Twelve different mutations were identified in our study, with R334W and R334Q being the most abundant, consistent with previous studies [16]. The relationship between genotype and phenotype has been a topic of interest. However, patients with the same mutation may presented with different time of disease onset and different clinical manifestation. Matsuda et al. evaluated the activity of NOD2 mutants in HEK 293 cells and found that the R331W mutant was a non-functional single-nucleotide polymorphism (SNP), while R334W, E383K, R587C, W490S, and D512V could cause spontaneous activation of the NF-κB pathway. When focusing on the relationship between genotype and phenotype, R587C variants was associated with relatively higher incidence of fever and R334W variants was associated with relatively higher incidence of skin and joint involvement [6]. In our study, R334Q was associated with arthritis, rash, uveitis and fever, whereas R334W was associated with

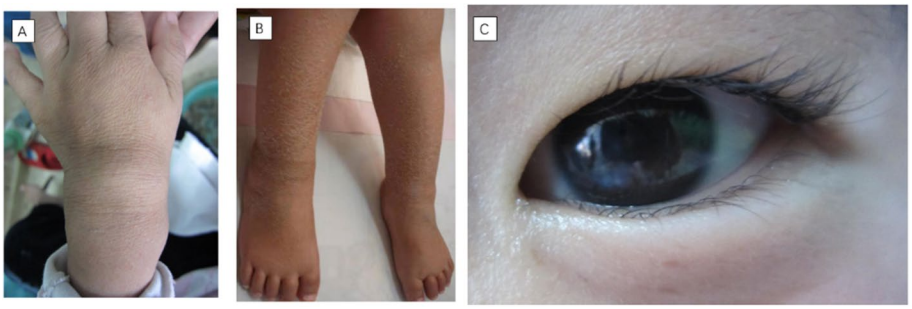

Fig. 2 Clinical triad of Blau syndrome in our center. **A** Boggy arthritis of Blau syndrome **B** Lichenoid-like rash of Blau syndrome **C** Uveitis of Blau syndrome

Table 2 Laboratory tests at disease initiation and follow-up visit

Laboratory tests	Disease initiation	Follow-up visit	t value	*P* value
C reactive protein mg/L	27.33 ± 5.53	6.06 ± 2.03	5.53	< 0.001
Erythrocyte sedimentation rate mm/h	30.23 ± 3.58	14.55 ± 2.39	5.46	< 0.001
Procalcitonin ng/ml	1.17 ± 0.76	0.43 ± 0.23	1.39	0.185
Ferritin ng/ml	47.98 ± 11.4	36.85 ± 9.63	3.65	0.001
Serum amyloid A protein μg/mL	12.8 ± 1.23	7.22 ± 0.64	7.34	< 0.001

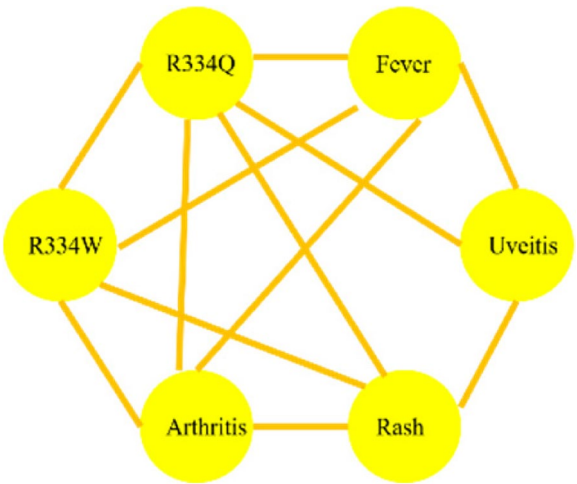

Fig. 3 Bayesian networks constructed with the correlation between genotype and phenotype

Table 3 Laboratory test before and after treatment of TNF-α inhibitors

Laboratory tests	At start of TNF-α inhibitors	At most recent follow-up	*P* value
C reactive protein mg/L	25.72 ± 4.4	3.13 ± 1.42	< 0.001
Erythrocyte sedimentation rate mm/h	27.39 ± 4.0	8.17 ± 2.11	< 0.001
Procalcitonin ng/ml	0.52 ± 0.25	0.14 ± 0.25	0.008
Ferritin ng/ml	33.58 ± 8.82	16.40 ± 2.50	0.001
Serun amyloid A protein μg/mL	19.63 ± 0.75	8.82 ± 1.48	< 0.001

arthritis, rash and fever. Differences between our study and Matsuda's study may be due to small sample size. Future studies should expand the sample size to better evaluate the relationship between genotype and phenotype. NOD2 genetic mutation leads to activation of NF-κ B pathway and release lots of inflammatory cytokines like tumor necrosis factor (TNF) and IL-1β. From this perspective, biologics may be useful in treatment of Blau syndrome. TNF-α inhibitors are usually the first choice. Previous studies have proved that TNF-α inhibitors combined with low dose of prednisolone and methotrexate yield satisfactory response [17]. Early biologics treatment could improve prognosis [6]. In our study, biologics treatments were tolerated. Biologics contributed to normalization of inflammatory indices, reduction of steroid dosage and increasing remission rate. Although biological treatments have potential benefits, more effective agents targeting different process of NF-κ B pathway are needed.

Prior reports found that median disease course of BS was 12.8 years and over 50% of patients had joint deformities. One-third of patients had normal function evaluated by childhood health assessment questionnaire (CHAQ) and health assessment questionnaire

(HAQ), one-third had mild impairment and one-third had moderate and severe impairment. Majority of patients with uveitis had active ocular involvement after 15 years of follow-up visits. Eye complications (e.g., cataracts and band keratopathy) were found in over one-third of patients and nearly two-third of patients had vision loss [18]. Biologics can initiate remission and reduce the incidence of complication. Median and the longest time of follow-up in our study were 40 months and 143 months. At the most recent follow-up visits, vast majority of patients reached the state of disease control but small amounts of patients still had joint contracture, skin lesions and active eye disease.

Our study is unique because it is the largest monocentric cohort study in China, and it describes the treatment response to TNF-α inhibitors through follow-up visits. Our study not only focuses on general clinical information but also on long term prognosis of these patients. Results of our study indicated that TNF- α inhibitors are promising in treatment of Blau syndrome. There are several limitations in our study. Since some clinical data were lacking, we could not assess normal growth, development and life quality of younger patient through CHAQ and HAQ. Future collaborations with other centers could expand the sample size and deepen our understanding of the disease.

Conclusion

Clinical manifestations of Blau syndrome are diverse and early diagnosis is crucial. Further studies are needed to elucidate the function of NOD2 mutations and the relationship between genotype and phenotype. Multicentric studies, especially international collaborations, are called for. TNF-α inhibitors are effective in normalizing inflammatory indices, reducing steroid dosages, and increasing remission rates. More targeted new drugs are needed for the treatment of Blau syndrome.

Abbreviations

BS	Blau syndrome
SE	Scaly erythematous
LP	Lichenoid papules
NSAIDs	Nonsteroidal anti-inflammatory drugs
DAG	Directed acyclic graph
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
SNP	Single-nucleotide polymorphism
TNF	Tumor necrosis factor
CHAQ	Childhood health assessment questionnaire
HAQ	Health assessment questionnaire

Acknowledgements

We thank all the participants and their parents of the study.

Authors' contributions

X.S. and J.D. contributed equally to this study.X.S. collected the data and wrote the draft. J.D. wrote the draft. C.L. provided the idea, provided critical comments and revised the manuscript.

Funding

There was no funding in this study.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This work was approved by Institutional Review Board of School of Public health, Capital Medical University, Beijing, China ([2022]-E-134-R). Written informed consent was obtained from participant and/or their parents.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 5 December 2024 Accepted: 11 March 2025
Published online: 11 May 2025

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