🩺 Physician Guide

Blau Syndrome: Quick Facts for Your Doctor

A Clinical Overview for Physicians and Specialists
Prepared by the Cure Blau Syndrome Foundation
Based on the Cure Blau Syndrome Foundation Round Table with Dr. Carlos D. Rose & Dr. Carine Wouters (June 5, 2023)

🔬 What is Blau Syndrome?

Blau Syndrome is a rare **monogenic autoinflammatory disease.** Previously, this mutation was thought to be caused by **gain-of-function mutations in the NOD2 gene,** however ongoing research is examining the function. This mutation leads to dysregulated innate immune activation. It presents early in life, typically before the age of 4, and is characterized by **non-caseating granulomatous inflammation** in multiple organ systems.

It is inherited in an **autosomal dominant** pattern but may also arise from de novo mutations or somatic mosaicism. When there is no family history, it may sometimes be called **Early-Onset Sarcoidosis (EOS)**.

🧬 Genetic Cause

- **NOD2 gene mutation** (most commonly at R334Q or R334W accounting for 70% of population)
- Mutations are localized near the **NACHT/NBD domain**, causing autonomous NOD2 signaling
- Confirm diagnosis via molecular testing (sequencing of NOD2)
- Additional identified variants include, but not limited to: D382N, E383K, L454V, G481D, W490L, C495Y, H520Y, R587C, E600A, E600K, Q809K

Miceli-Richard et al., (2001)
Saulsbury, Wouters, & Rose et al. (2009)

⚠ Classic Clinical Triad

1. **Granulomatous arthritis/tenosynovitis**
    - Symmetric, boggy joint swelling (esp. wrists, ankles)
    - Often misdiagnosed as JIA or RA
    - Camptodactyly may be present
    - Most involvement in PIP joints and tendon sheaths
    - Many adults misdiagnosed as sarcoidosis
    - Range of motion relatively preserved
2. **Uveitis**
    - Occurrence in 76% of Blau patients
    - Bilateral (97%) and chronic
    - Anterior, posterior, or panuveitis (55%)
    - High risk for complications (synechiae, cataracts, glaucoma, chorioretinal scarring)
    - Often leads to visual impairment or blindness if untreated
    - Typical fundus features of Blau posterior uveitis: pale optic disc, disc margins irregular, peripapillary pigement changes, nodular excrescensies (protrusions, bumps, prominences, swellings, border)
    - Multiple chorioretinal scars are visible
    - Most frequent anterior complications were cataract and synechiae (around 50%)
    - 25% increased intraocular pressure
    - One third of patients experienced moderate visual impairment already at baseline, with 15% of patients being legally blind
3. **Dermatitis**
    - Fine, scaly, monomorphic rash
    - Often appears in infancy or early childhood

🧠 Expanded Systemic Involvement

In up to 50% of cases, inflammation extends beyond the classic triad:

- Liver, kidney, large blood vessels
- Lymphadenopathy
- Pulmonary involvement
- Neurologic symptoms (rare)
- Fever, hypertension, central nervous system, cranial nerve, large vessel, small vessel, and erythema nodosum
- Patient reporting of diagnoses with dysautonomia and mast cell activation syndrome (source: Cure Blau Syndrome Foundation)

Source: **Blau International Registry & Cohort (Rose, Wouters, et al.)**

🧪 Diagnostic Workup

- **Genetic testing** for NOD2 mutation
- **Histopathology** (if biopsy): non-caseating granulomas
- **Ophthalmology evaluation** (slit lamp, fundus exam)
- **Imaging**: hand/wrist X-ray, chest X-ray if systemic symptoms
- **Laboratory**: CBC, ESR, CRP often normal; ACE may be normal or slightly elevated
- Consider urinalysis, liver and kidney function tests, echocardiogram

💊 Treatment Overview

1. Corticosteroids

- Oral (prednisone) for flares
- Topical or intraocular for uveitis

2. Immunomodulators

- Methotrexate, azathioprine, cyclosporine

3. Biologics

- **TNF inhibitors** (adalimumab, infliximab) – commonly used
- **IL-1 blockers** – less common
- **IL-17 inhibition** is under investigation
- New research into **PDE4 inhibitors** and NOD2-targeted therapies is ongoing

📈 Monitoring Recommendations

- **Rheumatology**: joint symptoms, mobility, growth
- **Ophthalmology**: full eye exams every 3–6 months
- **Referrals:** appropriate specialists as symptoms arise and may include pulmonology, orthopedics, nephrology, cardiology, etc.
- **General care**: BP, pulse, systemic signs
- **Labs**: CBC, ESR/CRP, LFTs, renal function
- Consider **imaging** (CXR, echocardiogram) based on symptoms

📌 Resources

- **Cure Blau Syndrome Foundation**: www.curebs.com
- **International Registry**: www.curebs.com/registry
- **Patient Webinar Recording**: Blau Syndrome Educational Forum Featuring Dr. Carlos Rose and Dr. Carine Wouters
- **Research Project Enrollment:** Dr. Ruth Napier, rnapier@cuanschutz.edu

For case discussions or collaborations, contact:
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Cure Blau Syndrome Foundation