

## Blau Syndrome: A Rare Multisystemic Genetic Disease with Distinctive Clinical Manifestations

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### ABSTRACT

Blau syndrome is an extremely rare genetic disease characterized by a multisystemic clinical presentation affecting the skin, joints, eyes and nervous system. It is an autosomal dominantly inherited disease caused by mutations in the NOD2/CARD15 gene. This disease predominantly affects children, although adult-onset cases have been reported. The epidemiology of Blau syndrome is limited due to its low prevalence, with fewer than 200 cases reported worldwide. Diagnosis is based on clinical evaluation and molecular genetic testing to identify mutations in the NOD2/CARD15 gene. Treatment focuses on symptom control and reduction of inflammation, using non-steroidal anti-inflammatory drugs, corticosteroids and, in more severe cases, immunosuppressive agents. Multidisciplinary collaboration between different medical specialties is essential for the comprehensive management of patients. Although advances have been made in the understanding of Blau syndrome, more research is still needed to elucidate its pathophysiology, epidemiology and therapeutic options.

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### INTRODUCTION

Blau syndrome, also known as chronic infantile granulomatosis syndrome, is a rare autosomal dominantly inherited genetic disease characterized by the presence of non-caseating granulomas in various tissues of the body. These granulomas are defined as chronic inflammatory aggregates composed of activated macrophages, multinucleated giant cells and lymphocytes, which form in response to a dysregulation of the immune response.<sup>1</sup>

At the molecular level, Blau syndrome is due to mutations in the NOD2/CARD15 gene, which encodes a protein belonging to the family of pattern recognition receptors (PRRs) and plays a key role in the detection of microbial pathogens. These mutations lead to abnormal and persistent activation of the nuclear factor kappa B (NF-κB) signaling pathway, a crucial intracellular cascade in the inflammatory response, resulting in exacerbated production of proinflammatory cytokines and granuloma formation.<sup>2</sup>

### Epidemiology

The epidemiology of Blau syndrome is quite limited due to its extreme rarity. The prevalence of this disease is estimated

to be extremely low, with less than 200 cases reported worldwide to date. In addition, a higher incidence of this disease has been observed in certain populations, such as descendants of European descent, although sporadic cases have been reported in other ethnicities.<sup>3</sup>

Blau syndrome typically presents in childhood, with most cases diagnosed before 5 years of age. However, late-onset cases have also been reported in adulthood. This disease has been observed to affect both males and females equally, with no clear predilection for a particular sex.<sup>4</sup>

Since Blau syndrome is a disease of genetic origin, it is considered an autosomal dominant disease, which implies that a single altered gene is sufficient to manifest the disease in an affected individual. However, sporadic cases with de novo mutations have been observed, meaning that the mutation occurs randomly in the affected individual, without being inherited from the parents.<sup>4</sup>

Due to the rarity of this disease and the lack of awareness about it, it is possible that there are undiagnosed or misdiagnosed cases, which could lead to an underestimation of its true prevalence. Therefore, further research and

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awareness is essential to better understand the epidemiology of Blau syndrome and its distribution in different populations.<sup>4</sup>

Blau syndrome is extremely rare and its prevalence is low. It mainly affects children, but can also occur in adults. It is seen in both sexes equally and a higher incidence has been identified in certain populations, especially in people of European descent. Given the rarity of the disease, further research is needed to fully understand its epidemiology and its impact on different population groups.<sup>5</sup>

### Clinic

Blau syndrome presents a varied and multisystemic clinical picture, affecting various organs and tissues of the body. Typical clinical symptoms are characterized by the presence of dermatological, articular, ocular and neurological manifestations.<sup>5,6</sup>

Regarding dermatological manifestations, patients with Blau syndrome usually present with skin lesions, ranging from papules, erythematous plaques to subcutaneous nodules. These lesions may appear on different areas of the body and are associated with localized inflammation. The presence of these cutaneous manifestations may be one of the first clinical signs of the disease.<sup>6</sup>

At the joint level, arthritis is a common manifestation of Blau syndrome. Patients may experience swelling, pain and stiffness in the affected joints, which can limit mobility and affect quality of life. Arthritis can be migratory, affecting different joints at different times, and can be symmetrical or asymmetrical in its presentation.<sup>6,7</sup>

Ocular involvement is another hallmark of Blau syndrome. Chronic anterior uveitis is the most common ocular manifestation, manifesting with ocular redness, pain, light sensitivity (photophobia) and blurred vision. Uveitis can be recurrent and can lead to serious complications such as cataracts, glaucoma and vision loss if not properly treated.<sup>7</sup>

Neurologically, Blau syndrome may present with various manifestations. Some patients may experience recurrent headaches, seizures, and neurological disturbances such as motor, sensory, or cognitive deficits. These neurological manifestations can vary in severity and clinical presentation, and may require specialized evaluation and management.<sup>7</sup>

In addition to the main clinical manifestations, other less frequent manifestations have been described in Blau syndrome, such as renal, gastrointestinal and cardiovascular involvement. However, these manifestations are less common and their frequency and severity vary among patients.<sup>8,9</sup>

Blau syndrome is characterized by a diverse and multisystemic clinical picture. Dermatologic, articular, ocular and neurologic manifestations are common in this disease. The presence of skin lesions, arthritis, uveitis and neurological manifestations should be evaluated and treated appropriately to control symptoms and prevent long-term complications. A multidisciplinary approach with specialists in dermatology, rheumatology, ophthalmology and

neurology is essential for the comprehensive management of patients with Blau syndrome.<sup>10</sup>

### Diagnosis

The diagnosis of Blau syndrome is based on a thorough clinical evaluation, as well as specific molecular genetic testing to identify mutations in the NOD2/CARD15 gene, which are characteristic of this disease.<sup>11</sup>

The diagnostic process begins with the detailed collection of the patient's medical history, including a family history of similar diseases and the identification of the characteristic symptoms of Blau syndrome, such as skin, joint, ocular and neurological manifestations.<sup>12</sup>

The next step is to perform a thorough physical examination, paying particular attention to skin lesions, the presence of arthritis and signs of uveitis. In addition, imaging tests such as X-rays, MRI or ultrasound may be performed to assess the status of the joints, central nervous system or other affected organs.<sup>12</sup>

Once Blau syndrome is suspected, molecular genetic testing for mutations in the NOD2/CARD gene is recommended.<sup>15</sup> These tests may include techniques such as DNA sequencing, polymerase chain reaction (PCR) or genetic linkage analysis, depending on availability and available resources.<sup>13</sup>

It is important to note that differential diagnosis is critical in Blau syndrome because of the similarity of symptoms to other inflammatory diseases such as sarcoidosis, Crohn's disease, and juvenile idiopathic arthritis. Therefore, these diseases should be carefully ruled out and complementary tests, such as histopathological studies of skin lesions and biopsies of affected organs, should be considered to differentiate Blau syndrome from other similar conditions.<sup>14</sup>

The diagnosis of Blau syndrome is based on a thorough clinical evaluation, including identification of characteristic clinical manifestations, followed by molecular genetic testing for mutations in the NOD2/CARD15 gene. Differential diagnosis and exclusion of other similar diseases are essential to establish an accurate and appropriate diagnosis. A multidisciplinary approach involving specialists in rheumatology, dermatology, ophthalmology and genetics is essential to reach an accurate diagnosis.<sup>14</sup>

### Treatment

Treatment of Blau syndrome is based on symptom control and reduction of systemic and localized inflammation. Since this disease is chronic and currently has no cure, the main goal of treatment is to improve the patient's quality of life and prevent long-term complications.<sup>15</sup>

In the therapeutic management of Blau syndrome, different pharmacological approaches are employed depending on the severity of symptoms and specific organ involvement. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) is considered an initial option to relieve joint pain and reduce inflammation. These medications may be useful in mild to moderate cases of arthritis and can be improved with

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adjunctive measures, such as physical therapy and local application of heat or cold.<sup>16</sup>

In cases of more severe symptoms or those resistant to NSAID treatment, oral or topical corticosteroids may be used. These drugs are effective in reducing the systemic or localized inflammatory response, and can be used for short periods of time to control acute flare-ups of inflammation. However, because of the long-term side effects of corticosteroids, it is recommended that the lowest possible dose be used and a gradual tapering is sought to minimize the associated risks.<sup>17</sup>

In cases of refractory or more severe symptoms, immunosuppressive agents may be considered. Methotrexate, azathioprine and calcineurin inhibitors such as tacrolimus are therapeutic options that can be used to reduce the inflammatory response and control symptoms. These drugs require regular monitoring of liver, renal and hematologic function due to potential adverse effects.<sup>16,17</sup>

In addition to pharmacological therapy, it is important to highlight the importance of a multidisciplinary approach in the management of Blau syndrome. The involvement of specialists such as rheumatologists, dermatologists, ophthalmologists and neurologists is essential to provide comprehensive care tailored to the individual needs of each patient. Physical therapy and occupational therapy can also play an important role in managing arthritis and improving functionality.<sup>17</sup>

Treatment of Blau's syndrome is based on symptom control and reduction of inflammation. The use of NSAIDs, corticosteroids and immunosuppressive agents is considered depending on the severity of symptoms and specific organ involvement. Physical therapy and occupational therapy may also be an integral part of management. A multidisciplinary approach and regular monitoring are essential to achieve adequate symptom control and prevent long-term complications.<sup>17</sup>

### CONCLUSIONS

In conclusion, Blau syndrome is an extremely rare genetic disease characterized by a multisystemic clinical presentation, including dermatologic, articular, ocular and neurologic manifestations. Its epidemiology is limited due to its low prevalence and lack of awareness of this disease. Diagnosis is based on detailed clinical evaluation and molecular genetic testing to identify mutations in the NOD2/CARD15 gene, which are characteristic of this disease. Treatment focuses on symptom control and reduction of inflammation, using non-steroidal anti-inflammatory drugs, corticosteroids and, in more severe cases, immunosuppressive agents. A multidisciplinary approach involving different medical specialties is essential to provide comprehensive care tailored to the individual needs of each patient. Given the rarity of this disease, further research and awareness is required to better understand its pathophysiology, epidemiology and therapeutic options.

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