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Distinguishing Blau Syndrome from Systemic Sarcoidosis

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Abstract

Purpose of Review: The purpose of this review is to provide a framework to distinguish Blau syndrome/Early Onset Sarcoidosis and Sarcoidosis clinically. We also discuss relevant differences in genetics, pathogenesis, and management of these diseases.

Recent Findings: Blau Syndrome and Sarcoidosis share the characteristic histologic finding of noncaseating granulomas as well as some similar clinical characteristics; nevertheless, they are distinct entities with important differences between them. Blau syndrome and Early Onset Sarcoidosis are due to one of numerous possible gain-of-function mutations in *NOD2*, commonly presenting before age 5 with a triad of skin rash, arthritis, and uveitis. However, as more cases are reported, expanded clinical manifestations have been described. In systemic Sarcoidosis, there are numerous susceptibility genes that have been identified, and disease is thought to result from an environmental exposure in a genetically susceptible host. It most often presents with constitutional symptoms and pulmonary involvement and typically affects adolescents and adults.

Summary: This paper reviews the similarities and differences between Blau syndrome and Sarcoidosis. We also discuss the importance of distinguishing between them, particularly with regard to prognosis and outcomes.

Keywords

Blau syndrome; Systemic Sarcoidosis; Sarcoidosis; NOD2 mutation

Introduction

Blau syndrome/Early Onset Sarcoidosis and systemic Sarcoidosis are chronic granulomatous conditions that share the common histologic feature of noncaseating granulomas, and both can affect similar organ systems. However, they differ in typical age at onset, genetics, and dominant clinical features.

Blau syndrome and Early Onset Sarcoidosis occur secondary to one of many possible single-gene mutations in *NOD2* and are classically characterized by the triad of skin rash, arthritis, and uveitis [1–5]. Blau syndrome and Early Onset Sarcoidosis refer to the autosomal dominantly inherited and sporadic forms of this condition, respectively, and

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will be referred to collectively as “Blau syndrome” throughout this review. Alternatively, systemic Sarcoidosis, referred to as “Sarcoidosis” throughout this review, is generally thought to occur due to a genetic predisposition and a secondary environmental exposure [6, 7]. About 90% of patients have pulmonary involvement, although skin, ocular, and musculoskeletal involvement are among the most common extrapulmonary features [6, 8–12]. Sarcoidosis, which is most commonly reported in adults, can certainly present in children, most commonly in adolescence, and similar to adults, constitutional symptoms and pulmonary involvement are the most common clinical features [13].

When evaluating patients, it is important to be able to distinguish between these two entities as they have different courses, genetic implications, treatment responses, and prognoses [11, 14–17]. In this review, we develop a framework for distinguishing these conditions clinically and also discuss important differences in genetics, pathogenesis, and treatment where relevant.

Body

Epidemiology

The incidence of Blau syndrome is unknown, but the annual incidence of combined granulomatous disorders (including Blau Syndrome, Early Onset Sarcoid, and Sarcoidosis) presenting before age 18 is reported to be 0.06–1.02/100,000 [6, 18]. Sarcoidosis presenting in adulthood is much more common with an overall annual incidence in the United States of 7.6–8.4/100,000 and prevalence of 59–60.1/100,000 [19].

Patients with Blau syndrome most commonly develop symptoms before the age of 5, although they may not be correctly diagnosed until later in life, particularly when the presentation lacks the characteristic triad of clinical manifestations, or the symptoms present sequentially rather than simultaneously [1, 4, 15, 17, 20, 21]. Earlier studies indicate that adults who develop Sarcoidosis most frequently present between 20 and 40 years of age, but more recent studies report that a substantial number of patients are diagnosed after 50 years of age, suggesting two peak ages at diagnosis [8, 19, 22]. Children that present with “adult-type” Sarcoidosis most commonly present in adolescence [13].

Children with Blau syndrome are most commonly of Asian, Caucasian, or Hispanic descent, whereas in “adult-type” Sarcoidosis presenting in childhood, 72–81% of patients are African American [4, 13, 15, 17, 21, 23–25]. In the United States, Sarcoidosis is more common in African American patients with an annual reported incidence of 17–71/100,000 compared to an annual incidence of 8–11/100,000 in white patients [9, 11, 19, 22].

Although not formally reported, there does not appear to be a difference in the ratio of females to males affected by Blau syndrome, likely because this is a monogenetic disease that is not sex-linked [4, 5, 15, 17, 21, 23, 25]. Sarcoidosis more commonly affects females than males, but males tend to present at a younger age, and in adolescents with Sarcoidosis, the ratio of male to female patients is approximately 1:1 [8, 11–13, 19, 26]. It should be noted, however, that many historical cohorts often include both Blau syndrome and juvenile

Sarcoidosis together in a single cohort making it difficult to differentiate clearly between the two [13, 26].

Pathogenesis

Genetics—Perhaps the most apparent difference between Blau syndrome and Sarcoidosis is that Blau syndrome is a monogenic autoinflammatory disease caused by one of at least 30 different known mutations in the *NOD2* gene, most commonly near the NOD/NACHT domain [2–5, 15, 17, 20, 21, 23]. The most common mutations are R334W and R334Q, occurring in 40–80% of patients [4, 5, 15, 17, 20, 21, 23]. Blau syndrome is inherited in an autosomal dominant fashion, whereas Early Onset Sarcoidosis is due to a sporadically occurring mutation in the same gene [1, 20, 27]. Although familial cases are transmitted in an autosomal dominant fashion, there have been reports of incomplete penetrance in association with the E383K mutation [17, 28, 29].

While there are some data that suggest the opposite, it is generally accepted now that the causative mutation in Blau syndrome is a gain-of-function mutation, located on or near domain interfaces in the NOD domain [20, 30, 31]. These regions stabilize the closed or inactive conformation of the NOD2 protein; therefore, mutations in these regions are hypothesized to destabilize the inactive conformation, leading to otherwise unstimulated protein activation [31, 32]. In contrast, the *NOD2* mutations found in Crohn's disease, another granulomatous inflammatory disease with predominantly gut but also ocular, skin, and joint involvement, are scattered throughout the gene, possibly affecting oligomer formation and ligand binding, consistent with the observation that *NOD2* mutations in Crohn's disease are considered to be loss-of-function mutations [31]. This discovery underscores the importance of the location of the NOD2 mutations in Blau syndrome as it relates to pathogenesis.

Alternatively, there are numerous susceptibility genes that have been associated with the development of Sarcoidosis. Sarcoidosis is traditionally thought to result from the combination of genetic predisposition plus an external stimulus [6, 7]. The influence of HLA genes and alleles are associated with the development of Sarcoidosis as well as the course and prognosis of the disease and may even differ by race [7, 33, 34]. For example, Lofgren's syndrome, an acute form of Sarcoidosis that presents with the triad of hilar adenopathy, arthralgia, and erythema nodosum, is associated with HLA-DRB1, and patients with the HLA-DRB1*03 allele have an especially good prognosis [35]. Other HLA genes associated with Sarcoidosis include HLA-DQA1, HLA-DRA, HLA-DRB5 [33]. Various other genes have been linked with the development of Sarcoidosis and include *ACE*, *ANXA11*, *BTNL2*, *LTA*, *MAPK*, *OS9*, *TAB1* and *TAB2* (a downstream gene associated with NOD2 protein signaling), and *TNFA* [33, 36–40].

Despite disease manifestations in similar organs, pathogenic *NOD2* mutations have not been observed in Sarcoidosis patients. Two recent studies evaluated adult Sarcoidosis patients with a similar pattern of organ involvement as patients with Blau syndrome for evidence of disease association with *NOD2* mutations [38, 41]. A combined cohort of 442 European American and 1273 African American sarcoidosis patients were genotyped for 23 genes within the *NOD2* pathway. No significant mutations in the *NOD2* gene were identified

in those with skin and bone/joint involvement; however, there were novel significant associations in four variants within the *TAB2* gene, suggesting the NOD2 pathway could be implicated in pathogenesis of Sarcoidosis [38]. In a genetic case-control study, 39 subjects with sarcoid-related uveitis were compared to 12 Sarcoidosis patients without ocular involvement. There were no significant differences in *NOD2* common variant allele frequencies, and none of the patients had pathogenic *NOD2* mutations associated with Blau syndrome, although 4 new non-synonymous *NOD2* variants were found in the ocular Sarcoidosis group that may have clinical significance [41].

Granuloma morphology—Blau syndrome and Sarcoidosis are both characterized by noncaseating granulomas on biopsy of affected tissues [6, 20, 30, 42]. In both diseases, granulomas are surrounded by a lymphocytic corona, contain an increased CD4+/CD8+ ratio, and contain multinucleated giant cells (MGCs) [7, 20, 30, 42]. Immunohistochemistry also shows elevated expression of IFN-γ, IL-17, IL-23R, and TNF-α [6, 7, 20, 30]. However, there are some important differences that can help differentiate histologically between the two conditions.

The lymphocytic corona surrounding granulomas in Blau syndrome is typically quite dense, whereas the corona surrounding granulomas in Sarcoidosis is thin [30]. Lymphocytic emperipolesis within MGCs is a prominent feature of Blau syndrome granulomas and is a distinguishing feature from granulomas in Sarcoidosis [30]. Emperipolesis may be associated with MGC death, resulting in fibrinoid necrosis observed in granulomas in Blau syndrome, whereas hyaline fibrosis is a common feature within granulomas in Sarcoidosis [30, 42]. While crystalline intracytoplasmic inclusions are rare in Blau syndrome granulomas, Sarcoid granulomas frequently contain various intracytoplasmic inclusions, such as Schaumann bodies, birefringent calcium oxalate crystals, cholesterol crystals, and asteroid bodies [30, 42].

Association with antigenic triggers—Antigenic triggers for granuloma formation have been associated with both Blau syndrome and Sarcoidosis. In Blau syndrome, disease onset or flare has been temporally associated with administration of the bacillus Calmette-Guerin (BCG) vaccine [17, 43]. Interferon gamma (IFN-γ) response to BCG vaccination is hypothesized to provide a stimulus for increased NOD2 production [17, 44]. Additionally, *Mycobacterium avium ss. paratuberculosis* (MAP), implicated as a cause of enteric granulomatous disease in ruminant animals and possibly Crohn's disease, has been speculated to be a trigger for Blau syndrome after DNA evidence of MAP was discovered in biopsy specimens from patients with Blau syndrome [45]. Altered host: microbial interactions are thought to play a role in this triggering phenomenon; cells with a Blau-associated *NOD2* defect exhibited poor intracellular clearance of *Salmonella typhimurium* and altered TNF-α expression compared to normal cells, which may play a role in the inflammatory response observed in Blau syndrome [46].

In Sarcoidosis, Mycobacteria and *Propionibacterium acnes*, in particular, have been implicated as antigenic triggers [7, 47, 48]. In a large systemic review and meta-analysis including 58 studies and over 6000 patients, there was a strong association between mycobacteria infection and Sarcoidosis [OR 6.8 (95% CI 3.73, 12.39)] [47]. A second

meta-analysis of case-control studies confirmed this association [48]. In the large systemic review and meta-analysis by Esteves et al, an etiologic link between infection with *Propionibacterium acnes* and Sarcoidosis was also observed [OR 18.80 (95% CI 12.62, 28.01)] [47]. *NOD1* gene polymorphisms (796G/A and 796A/A) were associated with impaired response to intracellular *P. acnes* through diminished NF-κB activation and development of Sarcoidosis in Japanese patients, suggesting a genetic link to pathogenesis [49]. This association has not been studied in Blau syndrome.

Although the specific mechanisms remain to be elucidated, it is clear that an aberrant immune response to variety of antigenic factors lead to the common endpoint of granuloma formation in both Blau syndrome and Sarcoidosis.

Disease Manifestations

Edward Blau originally described eleven family members over four generations presenting with granulomatous arthritis, uveitis, and/or rash [1]. Two of these patients presented with all three clinical features. Collectively, these features are considered to be the classic triad of Blau syndrome and are present together in various degrees in different cohorts [1, 4, 5, 15, 17, 21]. Symptoms generally present before age 5, with rash typically presenting earliest and may be misdiagnosed without concomitant development of the other symptoms [1, 4, 15, 17, 20, 21]. In recent years, clinical manifestations beyond the classic triad have been reported [4, 5, 17, 21, 25, 50]. For example, pulmonary involvement with interstitial lung disease (ILD) in Blau syndrome is rare but can occur [5, 21, 50, 51]. In contrast, approximately 90% of patients with Sarcoidosis have pulmonary involvement, ranging from adenopathy to interstitial lung disease [6, 10–12]. Some of the most common extrapulmonary manifestations in Sarcoidosis involve the musculoskeletal, ocular, and dermatologic systems. Although both Blau syndrome and Sarcoidosis share involvement of many of the same organ systems, the manifestations remain clinically distinct.

Arthritis—In Blau syndrome, arthritis is usually the most common manifestation, either alone or in combination with other features [1, 15, 17, 21, 25]. Except in one cohort in which 73% of patients were affected by arthritis, most cohorts report that greater than 90% of patients have arthritis [4, 5, 17, 21, 23, 25]. The arthritis is characteristically in a polyarticular pattern involving small and large joints, often affecting the wrists, proximal interphalagneal (PIP) joints, knees, and ankles [1, 4, 17, 21]. Oligoarthritis may occur but is the pattern of presentation in less than one-quarter of patients [4, 17, 21]. The arthritis is described as “boggy” and characteristically causes exuberant tenosynovitis [4, 5, 23]. Interestingly, range of motion is generally preserved until late in the disease course [1, 20]. Erosive disease, while it can occur, is rare, but other dysplastic changes, including carpal dysplasia, biconcave radius, plump ulna, and abnormal shape of the second metacarpal, are relatively common [1, 20, 52, 53]. Camptodactyly is an especially common feature of Blau syndrome, present in roughly 60% of patients [4, 21, 54]. These dysplastic changes can be helpful for diagnosis when observed on x-ray [21].

Arthritis or arthralgia occurs in about 5–15% of patients with Sarcoidosis [12]. The arthritis in Sarcoidosis presents most commonly in a symmetric oligoarticular pattern, in contrast

to the polyarthritis seen in Blau syndrome [11, 35, 55]. Bilateral ankle swelling has been reported in the vast majority of patients with arthritis in one study [55]. Similar to Blau syndrome, erosive disease is uncommon in Sarcoidosis; however, in contrast to Blau syndrome, camptodactyly is rare and dactylitis common in Sarcoidosis [35, 54].

Dermatologic manifestations—Although the skin is involved in both Blau syndrome and Sarcoidosis, the clinical manifestations are quite distinct in each condition. In Blau syndrome, the skin rash is often the first symptom to develop, generally occurring within the first 1–2 years of life, and is the second most common symptom in most cohorts, affecting about 70–90% of patients [1, 4, 15, 17, 20, 21, 43]. The characteristic rash is described as scaly, erythematous or flesh-colored fine papules or coalescent plaques, often becoming more tan-colored, “dirty”, or scaly appearing with longer disease duration [1, 17, 20, 43]. The rash is not painful, is infrequently pruritic, and may be widespread [17, 43]. Unsurprisingly, skin biopsy shows noncaseating granulomas [1, 20]. Other skin rashes observed less commonly and often later in the course of disease include erythema nodosum, leukocytoclastic vasculitis, and livedoid-type rashes [17, 21, 43]. Skin manifestations may resolve spontaneously within 5 years or continue to flare over the course of the disease [43].

In Sarcoidosis, the skin is the most commonly involved extrathoracic site with 20–30% of patients affected [8–11]. Sarcoidosis-specific lesions demonstrate noncaseating granulomas on biopsy and include subcutaneous nodules, papules, plaques, tattoo or scar sarcoidosis, lupus pernio, and ulcerations; subcutaneous nodules and papules and plaques are most common [12, 56]. The papules and plaques may be similar in color, but larger than the millimetric papules seen in Blau syndrome. Erythema nodosum, histologically described as a septal panniculitis, is a non-specific lesion that occurs in almost 10% of Sarcoidosis patients and can occur specifically as part of Lofgren syndrome [8, 12, 56]. Similar to other manifestations of Sarcoidosis and to skin involvement in Blau syndrome, skin lesions may resolve spontaneously.

Uveitis—Uveitis is the least common of the classic manifestations of Blau syndrome, occurring in about 60–80% of patients, but is responsible for significant disease-related morbidity [4, 5, 17, 21, 23]. When it occurs, uveitis typically appears latest and is difficult to treat, with the majority of patients requiring therapy for ongoing active inflammation 5 years after uveitis onset [4, 15, 20, 21, 57]. Bilateral panuveitis is the most common presentation, though isolated anterior, intermediate, and posterior uveitis can also occur [1, 4, 5, 17, 21, 23, 25]. The frequency of long-term morbidity is unfortunately high in those affected by ocular inflammation, with about 30% of patients with uveitis developing moderate to severe visual impairment [15, 21]. In one study, patients with R334W and R334Q mutations, the most commonly reported Blau mutations, had less visual acuity loss than those with all other mutations combined [15]. Common uveitis complications include band keratopathy, posterior synechiae, increased intraocular pressure, and cataracts [15, 21]. Other ocular manifestations include optic disc pallor, peripapillary nodules, optic disc edema, macular edema, nummular corneal subepithelial deposits, and multifocal chorioretinal lesions [15, 25].

Up to 80% of patients with Sarcoidosis may have ocular involvement, though most studies report a range of about 10–30% [6, 8–12, 58]. Uveitis is the most common ocular manifestation [6, 12, 58]. In contrast to Blau syndrome, anterior uveitis is the most common presentation observed in Sarcoidosis, but up to 25% of patients may also have posterior involvement [6, 12, 58]. Panuveitis and posterior uveitis are more common in black patients than in white patients, a distinction not noted in Blau syndrome [12]. Ocular manifestations distinct from Blau include scleritis, episcleritis, lacrimal gland involvement, orbital masses, and optic neuritis [12]. Another important distinction between ocular involvement in Blau syndrome and Sarcoidosis is that the visual outcome of uveitis in Sarcoidosis tends to be favorable [12].

Pulmonary—The first case of Blau syndrome-associated ILD was reported in 2007 [50]. The patient presented with arthritis at 1 year of age and bilateral anterior uveitis at 3 years of age. At 16 years of age, he subsequently developed cervical lymphadenopathy, and computed tomography (CT) of the chest showed axillary and mild mediastinal lymphadenopathy as well as small areas of ground glass opacity. ILD has been reported in six additional patients [21, 51]. In at least two of the cases, imaging and symptoms resolved or improved with treatment [50, 51]. Pulmonary outcomes were not reported in the other patients [21]. Whereas pulmonary involvement is rare in Blau syndrome, the lung is the most commonly involved organ in Sarcoidosis, affecting at least 90% of patients in most cohorts [8–11]. Stage I (hilar enlargement only) and stage II (hilar enlargement plus intraparenchymal disease) disease are the most common presentations [8, 9, 11]. Up to half of patients are asymptomatic with regard to lung disease at presentation, though patients may present with shortness of breath, dyspnea on exertion, chest tightness, or cough [6, 9, 11, 12]. If Sarcoidosis is suspected, imaging by CT scan to evaluate for pulmonary involvement is recommended [11]. Depending on the stage of disease at presentation, outcomes of pulmonary Sarcoidosis may be very good, particularly patients with stage I disease. Even a majority of patients who have stage II-IV disease may have radiographic improvement without therapy or remain asymptomatic [14]. Up to 70% of patients may require systemic therapy for symptomatic pulmonary disease, but only about half of those require treatment for more than two years, the majority of whom can be maintained on low-dose therapy [14].

Other clinical features—About one-third to one-half of patients with Blau syndrome have manifestations beyond the classic triad [4, 5, 20, 21]. Similar to other autoinflammatory conditions, fever, either recurrent or persistent, is not uncommon [4, 5, 17, 21, 25]. Involvement of the reticuloendothelial system with lymphadenopathy, hepatomegaly, and/or splenomegaly can occur [4, 5, 17, 21, 23]. Severe hypertension has been reported in several case series, attributed to nonvascular renal disease, large vessel vasculitis with renal artery involvement, vasculopathy of intermediate-sized renal vessels, and chronic steroid use [4, 5, 17, 21]. A rare but serious manifestation is large vessel vasculitis, including aortitis and Takayasu’s-like arteritis [20]. Other expanded manifestations include cranial neuropathies (especially transient facial palsy), ischemic stroke, sialadenitis, pulmonary embolism, cardiomyopathy, granulomatous interstitial nephritis, nephrocalcinosis, granulomatous glomerulonephritis, and granulomatous hepatitis

[4, 5, 17, 21, 23, 57, 59–61]. Hypercalcemia in association with nephrocalcinosis and osteosclerosis has also been reported [62]. Therefore, neither the lack of the complete triad nor the presence of additional manifestations, including those more commonly seen in Sarcoidosis, such as hypercalcemia and pulmonary disease, should rule out Blau syndrome as a diagnosis. Furthermore, remaining vigilant for signs of other rare but serious disease manifestations is imperative.

As noted above, skin, eye, and joint involvement are common extrathoracic manifestations of Sarcoidosis, and some clinical features overlap in both conditions as discussed above. Clinically apparent cardiac involvement is present in up to 5% of Sarcoidosis patients, with symptoms and signs including palpitations, heart failure, and arrhythmias [4–6, 8–12, 17, 60, 61]. Cardiac granulomas are found in up to 25% of Sarcoidosis in post-mortem studies [6]. Hypercalcemia may affect as many as 40% of patients with Sarcoidosis, and pediatric patients diagnosed with Sarcoidosis may be more likely to have hypercalcemia than their adult counterparts [6, 63]. Neurologic manifestations affect up to 25% of patients with Sarcoidosis, much more frequently than in Blau syndrome, and have a wider variety of presentations beyond cranial neuropathy, including seizures and meningeal or white matter disease, leading to headache, ataxia, cognitive dysfunction [6, 8–12, 20, 64]. Aortitis has been reported rarely in association with both conditions, so while it is important to be aware of this rare association, this is not a distinguishing factor between the two conditions [17, 26, 60, 61, 65–68].

Diagnosis

The diagnosis of Blau syndrome is made when patients present with classical clinical features and can be confirmed by genetic testing and biopsy. Genetic testing for common genetic variants is commercially available. Synovial and skin biopsies are most commonly done to look for noncaseating granulomas, but the yield is higher with skin biopsy [20, 30, 43].

Laboratory and imaging studies can be supportive but are usually not diagnostic. Elevated erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) levels are non-specific and may be normal [1, 4, 59]. Hypercalcemia is significantly less likely in Blau syndrome but has been reported [20, 62, 69]. Serum angiotensin converting enzyme (ACE) levels are mostly reported to be normal, though elevated ACE levels have been seen [1, 26, 59]. ACE is produced by the epithelioid cells and macrophages of the granuloma; therefore, any granulomatous disease could result in elevated ACE levels, making this a nonspecific test for the diagnosis of Blau syndrome. Furthermore, normal serum ACE levels differ by age, so this is an important consideration when interpreting the serum ACE level in children [70, 71]. Hand and wrist x-rays may show dysplastic changes, including camptodactyly, carpal dysplasia, abnormal distal radial epiphysis, abnormal distal ulna shape, short ulna, abnormal shape of the second metacarpal bone, and these features may help differentiate Blau syndrome from Sarcoidosis [21]. Patients suspected to have Blau syndrome should have an ophthalmologic exam to assess for uveitis.

Similarly, the diagnosis of Sarcoidosis is made on the basis of a compatible clinical and radiographic presentation, and exclusion of other differential diagnoses [6, 12, 22,

41]. Biopsy for histologic confirmation is preferred when feasible, and beyond the lungs, additional locations to consider for biopsy include lacrimal glands and peripheral lymph nodes. Serum ACE levels are elevated in as many as three-quarters of sarcoidosis patients, which is significantly higher than in patients with Blau syndrome [6, 72]. However, sensitivity of the serum ACE level is generally low, ranging from 41.4–78.1% with specificity ranging from 76–90% [72–74]. In two different populations, the positive predictive value ranged from 10–25.4% and the negative predictive value ranged from 89.9–96.6%, making an elevated serum ACE level not particularly helpful in diagnosing either condition [72, 73].

Prognosis and Treatment

There is a significant difference in prognosis between Blau syndrome and Sarcoidosis, and this subsequently impacts the choice and duration of treatments used in each condition. One international prospective cohort study in 31 Blau syndrome patients found that after a median disease duration of 12.8 years, active arthritis or active uveitis requiring ongoing immunosuppressive therapy was observed in nearly 100% of patients; more than half had reduced functional capacity based on childhood health assessment questionnaires (CHAQ) and health assessment questionnaires (HAQ), and a third had had moderate or severe visual loss [21]. Another study reported blindness in 14% of patients [17]. In contrast, more than 50% of Sarcoidosis patients achieve remission within three years, and two-thirds of Sarcoidosis patients achieve remission after a decade, with few or no long-term sequelae [6]. Visual and musculoskeletal outcomes are generally good with most patients having non-progressive disease [11, 35]. Those that require chronic immunosuppressive therapy can often be maintained on relatively low doses of medication, and even the majority of patients with pulmonary involvement may not require any treatment, if asymptomatic, regardless of more advanced (stages II-IV) disease [12, 14].

Blau syndrome requires systemic immunosuppressant therapy to manage the ocular and musculoskeletal manifestations of this disease, and therapeutic choices are driven by the organ system involved and the severity of involvement. Treatments include systemic steroids, topical steroids, disease modifying antirheumatic drugs (DMARDs), biologic agents, and combination of multiple therapies [1, 4, 15, 17, 21, 23, 25, 50, 59, 75–83]. In more recently reported Blau cohorts, 70% of patients were treated with a combination of systemic steroid plus conventional DMARD, systemic steroid plus a biologic, or a conventional DMARD plus a biologic, yet despite aggressive combination therapy, disease remained overwhelmingly active [15, 17, 21].

In Blau syndrome, anti-TNF-α agents are the most commonly used biologic class, with the most success achieved with monoclonal antibodies adalimumab (ADA) or infliximab (IFX) [15, 17, 20, 21, 24, 25, 50, 57, 62, 76, 77, 81–86]. TNF-α helps with macrophage remodeling and formation of multinucleated giant cells, leading to development of mature granulomas; therefore, the use of anti-TNF-α agents disrupts this process and can treat granulomatous inflammation [87]. Interleukin-1 (IL-1), a downstream product of NOD2 activation, is elevated in some patients with Blau syndrome, and anti-IL-1 therapy has been tried with varying success, often, but not always, following anti-TNF-α therapy [4, 15, 21,

75, 83, 86]. Similarly, IL-6, another downstream product of NOD2 activation, is elevated in some patients with Blau syndrome, and anti-IL-6 therapy, following anti-TNF-α therapy, has also been used periodically with varying success [4, 78, 80].

In contrast, a study of 500 patients from Sarcoidosis centers across the world revealed that only 43% of patients were still on therapy five years after diagnosis [14, 88]. Up to two-thirds of patients with pulmonary Sarcoidosis may not require any systemic therapy or can be managed on a low-dose regimen of up to 15mg/day of prednisone [9–12, 14, 88, 90]. As in Blau syndrome, disease manifestations drive choice of therapy. Systemic corticosteroids are first-line therapy for symptomatic pulmonary involvement, skin involvement, and hepatic involvement [12]. As such, they are the most common medication used, chosen in up to 90% of treated patients [9–11, 14, 90]. DMARDs, most commonly methotrexate, are typically used as second-line agents for disease that does not respond to systemic corticosteroids [9, 10, 12, 90]. Studies show about 60–80% response to methotrexate for pulmonary, cutaneous, ocular, and neurologic manifestations [14]. Biologic agents are third-line therapy and are used much less frequently in Sarcoidosis, about 5% of patients [12, 90]. As in Blau syndrome, anti-TNF-α agents are the most commonly used biologic class used in Sarcoidosis [90]. A recent systematic review evaluated both randomized and non-randomized studies utilizing anti-TNF-α agents for different manifestations of Sarcoidosis, revealing overall safety and efficacy of Infliximab and Adalimumab for various clinical manifestations of Sarcoidosis [16].

Conclusions

Blau syndrome and Sarcoidosis share several overlapping features, most notably the finding of noncaseating granulomas in affected tissues and disease that often affects the same organ systems. However, Blau syndrome is more refractory to treatment; therefore, patients are at higher risk for chronic morbidity and poor long-term outcomes. Recognizing the distinguishing features of these diseases is paramount in differentiating these conditions from each other and from other mimickers.

Despite at times a blurred distinction between these granulomatous disorders, it is possible to distinguish their unique clinical characteristics through a thorough physical exam, as the clinical features in each condition are quite distinct, even when they occur in the same organ system. A biopsy is often necessary to confirm the diagnosis of a granulomatous disorder, and specific histologic features may also be useful to help differentiate between Blau syndrome and Sarcoidosis; however, it is genetic testing that often confirms the diagnosis of Blau syndrome. Genetic testing is not as useful diagnostically for Sarcoidosis, but as we learn more in this domain, we will likely utilize genetic testing to help stratify disease course and prognosis in both conditions.

In summary, Blau syndrome and Sarcoidosis remain linked by the histologic presence of the granuloma, and although both share some overlapping clinical features, there remain unique clinical manifestations in each condition to guide the astute clinician. Due to the disparate prognosis and outcomes in each condition, it is imperative to differentiate early, to initiate

appropriate therapy, manage co-morbidities, and optimize long-term outcomes for children and adults alike.

Disclosures:

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References

1 •. Blau EB Familial granulomatous arthritis, iritis, and rash. J Pediatr. 1985;107(5):689–693. doi:10.1016/S0022-3476(85)80394-2. [PubMed: 4056967] First published description of familial granulomatous disease, later named Blau syndrome.

2. Tromp G, Kuivaniemi H, Raphael S, et al. Genetic linkage of familial granulomatous inflammatory arthritis, skin rash, and uveitis to chromosome 16. Am J Hum Genet. 1996;59(5):1097–1107. [PubMed: 8900239]

3. Miceli-Richard C, Lesage S, Rybojad M, et al. CARD15 mutations in Blau syndrome. Nat Genet. 2001;29(1):19–20. doi:10.1038/ng720. [PubMed: 11528384]

4. Aróstegui JI, Arnal C, Merino R, et al. NOD2 gene-associated pediatric granulomatous arthritis: Clinical diversity, novel and recurrent mutations, and evidence of clinical improvement with interleukin-1 blockade in a Spanish cohort. Arthritis Rheum. 2007;56(11):3805–3813. doi:10.1002/art.22966. [PubMed: 17968944]

5. Rosé CD, Aróstegui JI, Martin TM, et al. NOD2-Associated pediatric granulomatous arthritis (PGA): an expanding phenotype. A study of an international registry and a national cohort. Arthritis Rheum. 2009;60(6):1797–1803. [PubMed: 19479837]

6. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007;357:2153–2165. doi:10.1056/NEJMra071714. [PubMed: 18032765]

7. Bennett D, Bargagli E, Refini RM, Rottoli P. New concepts in the pathogenesis of sarcoidosis. Expert Rev Respir Med. 2019;13(10):981–991. doi:10.1080/17476348.2019.1655401. [PubMed: 31414923]

8. Baughman RP, Teirstein AS, Judson MA, et al. Clinical Characteristics of Patients in a Case Control Study of Sarcoidosis. Am J Respir Crit Care Med. 2001;164:1885–1889. doi:10.1164/rccm2104046. [PubMed: 11734441]

9. Cozier YC, Berman JS, Palmer JR, Boggs DA, Serlin DM, Rosenberg L. Sarcoidosis in black women in the United States: Data from the Black Women's Health Study. Chest. 2011;139(1):144–150. doi:10.1378/chest.10-0413. [PubMed: 20595459]

10. Judson MA, Boan AD, Lackland DT. The Clinical Course of Sarcoidosis: Presentation, Diagnosis, and Treatment in a Large White and Black Cohort in the United States. Sarcoidosis Vasc Diffus Lung Dis. 2012;29:119–127.

11. Ungprasert P, Crowson CS, Matteson EL. Epidemiology and clinical characteristics of sarcoidosis: An update from a population-based cohort study from Olmsted County, Minnesota. Reumatismo. 2017;69(1):16–22. doi:10.4081/reumatismo.2017.965. [PubMed: 28535617]

12 •. Ungprasert P, Ryu JH, Matteson EL. Clinical Manifestations, Diagnosis, and Treatment of Sarcoidosis. Mayo Clin Proc Innov Qual Outcomes. 2019;3(3):358–375. doi:10.1016/j.mayocpiqo.2019.04.006. [PubMed: 31485575] A thorough and updated review about sarcoidosis.

13. Shetty AK, Gedalia A. Childhood sarcoidosis: A rare but fascinating disorder. Pediatr Rheumatol. 2008;6:1–10. doi:10.1186/1546-0096-6-16.

14. Baughman RP, Nunes H. Therapy for sarcoidosis: Evidence-based recommendations. Expert Rev Clin Immunol. 2012;8(1):95–103. doi:10.1586/eci.11.84. [PubMed: 22149344]

15. Sarens IL, Casteels I, Anton J, et al. Blau Syndrome–Associated Uveitis: Preliminary Results From an International Prospective Interventional Case Series. Am J Ophthalmol. 2018;187:158–166. doi:10.1016/j.ajo.2017.08.017. [PubMed: 28887115]

16. Adler BL, Wang CJ, Bui TL, Schilperoort HM, Armstrong AW. Anti-tumor necrosis factor agents in sarcoidosis: A systematic review of efficacy and safety. Semin Arthritis Rheum. 2019;48(6):1093–1104. doi:10.1016/j.semarthrit.2018.10.005. [PubMed: 30446173]

17 •. Matsuda T, Kambe N, Ueki Y, et al. Clinical characteristics and treatment of 50 cases of Blau syndrome in Japan confirmed by genetic analysis of the NOD2 mutation. Ann Rheum Dis. 2020:1–8. doi:10.1136/annrheumdis-2020-217320.A recent study describing a large cohort of Blau syndrome patients.

18. Chiu B, Chan J, Das S, Alshamma Z, Sergi C. Pediatric sarcoidosis: A review with emphasis on early onset and high-risk sarcoidosis and diagnostic challenges. Diagnostics. 2019;9(4):1–13. doi:10.3390/diagnostics9040160.

19. Baughman RP, Field S, Costabel U, et al. Sarcoidosis in America: Analysis based on health care use. Ann Am Thorac Soc. 2016;13(8):1244–1252. doi:10.1513/AnnalsATS.201511-760OC. [PubMed: 27509154]

20 •. Wouters CH, Maes A, Foley KP, Bertin J, Rose CD. Blau Syndrome, the prototypic auto-inflammatory granulomatous disease. Pediatr Rheumatol. 2014;12(1):1–9. doi:10.1186/1546-0096-12-333r5.Excellent review about Blau syndrome, addressing presentation, genetics, histology.

21 ••. Rosé CD, Pans S, Casteels I, et al. Blau syndrome: Cross-sectional data from a multicentre study of clinical, radiological and functional outcomes. Rheumatol (United Kingdom). 2015;54(6):1008–1016. doi:10.1093/rheumatology/keu437.Recent, multicenter study addressing presentation and outcomes.

22. Gerke AK, Judson MA, Cozier YC, Culver DA, Koth LL. Disease burden and variability in sarcoidosis. Ann Am Thorac Soc. 2017;14:S421–S428. doi:10.1513/AnnalsATS.201707-564OT. [PubMed: 29087725]

23. Rosé CD, Wouters CH, Meiorin S, et al. Pediatric granulomatous arthritis: An international registry. Arthritis Rheum. 2006;54(10):3337–3344. doi:10.1002/art.22122. [PubMed: 17009307]

24. Imayoshi M, Ogata Y, Yamamoto S. A Case of Sporadic Blau Syndrome with an Uncommon Clinical Course. Case Rep Rheumatol. 2018;2018:1–5. doi:10.1155/2018/6292308.

25. Nascimento H, Sousa JM, Fernández DG, et al. Blau-Jabs syndrome in a tertiary ophthalmologic center. Ophthalmic Surg Lasers Imaging Retin. 2018;49(1):70–75. doi:10.3928/23258160-20171215-12.

26. Gedalia A, Khan TA, Shetty AK, Dimitriades VR, Espinoza LR. Childhood sarcoidosis: Louisiana experience. Clin Rheumatol. 2016;35(7):1879–1884. doi:10.1007/s10067-015-2870-9. [PubMed: 25616361]

27. Kanazawa N, Okafuji I, Kambe N, et al. Early-onset sarcoidosis and CARD15 mutations with constitutive nuclear factor-κB activation: Common genetic etiology with Blau syndrome. Blood. 2005;105(3):1195–1197. doi:10.1182/blood-2004-07-2972. [PubMed: 15459013]

28. Saulsbury FT, Wouters CH, Martin TM, et al. Incomplete penetrance of the NOD2 E383K substitution among members of a pediatric granulomatous arthritis pedigree. Arthritis Rheum. 2009;60(6):1804–1806. doi:10.1002/art.24532. [PubMed: 19479836]

29. Harada J, Nakajima T, Kanazawa N. A Case of Blau Syndrome with NOD2 E383K Mutation. Pediatr Dermatol. 2016;33(6):e385–e387. doi:10.1111/pde.12908. [PubMed: 27339507]

30. Janssen CEI, Rose CD, De Hertogh G, et al. Morphologic and immunohistochemical characterization of granulomas in the nucleotide oligomerization domain 2-related disorders Blau syndrome and Crohn disease. J Allergy Clin Immunol. 2012;129(4):1076–1084. doi:10.1016/j.jaci.2012.02.004. [PubMed: 22464675]

31. Maekawa S, Ohto U, Shibata T, Miyake K, Shimizu T. Crystal structure of NOD2 and its implications in human disease. Nat Commun. 2016;7(May):1–11. doi:10.1038/ncomms11813.

32. Thirumal Kumar D, Udhaya Kumar S, Nishaat Laeeque AS, et al. Computational Model to Analyze and Characterize the Functional Mutations of NOD2 Protein Causing Inflammatory Disorder – Blau Syndrome. Vol 120. Elsevier Ltd; 2020. doi:10.1016/bs.apcsb.2019.11.005.

33. Adrianto I, Lin CP, Hale JJ, et al. Genome-wide association study of African and European Americans implicates multiple shared and ethnic specific loci in sarcoidosis susceptibility. PLoS One. 2012;7(8):1–10. doi:10.1371/journal.pone.0043907.

34. Levin AAM, Adrianto I, Datta I, et al. Association of HLA-DRB1 with sarcoidosis susceptibility and progression in African Americans. Am J Respir Cell Mol Biol. 2015;53(2):206–216. doi:10.1165/rcmb.2014-0227OC. [PubMed: 25506722]
35. Bechman K, Christidis D, Walsh S, Birring SS, Galloway J. A review of the musculoskeletal manifestations of sarcoidosis. Rheumatology (Oxford). 2018;57(5):777–783. doi:10.1093/rheumatology/kex317. [PubMed: 28968840]
36. Hofmann S, Fischer A, Nothnagel M, et al. Genome-wide association analysis reveals 12q13.3-q14.1 as new risk locus for sarcoidosis. Eur Respir J. 2013;41(4):888–900. doi:10.1183/09031936.00033812. [PubMed: 22936702]
37. Song GG, Kim JH, Lee YH. Associations between TNF-α −308 A/G and lymphotoxin-α +252 A/G polymorphisms and susceptibility to sarcoidosis: A meta-analysis. Mol Biol Rep. 2014;41(1):259–267. doi:10.1007/s11033-013-2859-x. [PubMed: 24197700]
38. Bello GA, Dumancas GG, Levin AM, Iannuzzi MC, Rybicki BA, Montgomery C. Role of NOD2 Pathway Genes in Sarcoidosis Cases with Clinical Characteristics of Blau Syndrome. 2015:1133–1135. doi:10.1007/978-90-481-8566-5_5.
39. Lin Y, Wei J, Fan L, Cheng D. BTNL2 gene polymorphism and sarcoidosis susceptibility:A meta-analysis. PLoS One. 2015;10(4):1–10. doi:10.1371/journal.pone.0122639.
40. Song GG, Kim JH, Lee YH. Associations between the angiotensin-converting enzyme insertion/deletion polymorphism and susceptibility to sarcoidosis: A meta-analysis. JRAAS - J Renin-Angiotensin-Aldosterone Syst. 2015;16(1):219–226. doi:10.1177/1470320313489059. [PubMed: 23676252]
41. Davoudi S, Navarro-Gomez D, Shen L, et al. NOD2 genetic variants and sarcoidosis-associated uveitis. Am J Ophthalmol Case Reports. 2016;3:39–42. doi:10.1016/j.ajoc.2016.05.005.
42. Rossi G, Cavazza A, Colby TV. Pathology of Sarcoidosis. Clin Rev Allergy Immunol. 2015;49(1):36–44. doi:10.1007/s12016-015-8479-6. [PubMed: 25762348]
43 ••. Poline J, Fogel O, Pajot C, et al. Early-onset granulomatous arthritis, uveitis and skin rash: characterization of skin involvement in Blau syndrome. J Eur Acad Dermatology Venereol. 2020;34(2):340–348. doi:10.1111/jdv.15963.Excellent review of the cutaneous manifestations of Blau syndrome.
44. Takada S, Kambe N, Kawasaki Y, et al. Pluripotent stem cell models of Blau syndrome reveal an IFN-γ–dependent inflammatory response in macrophages. J Allergy Clin Immunol. 2018;141(1):339–349.e11. doi:10.1016/j.jaci.2017.04.013. [PubMed: 28587749]
45. Dow CT, Ellingson JLE. Detection of Mycobacterium avium ss. paratuberculosis in Blau syndrome tissues. Autoimmune Dis. 2010;1(1). doi:10.4061/2010/127692.
46. Kim T-H, Payne U, Zhang X, et al. Altered host:pathogen interactions conferred by the Blau syndrome mutation of NOD2. Rheumatol Int. 2007;27(3):257–262. doi:10.1007/s00296-006-0250-0. [PubMed: 17096091]
47. Esteves T, Aparicio G, Garcia-Patos V. Is there any association between Sarcoidosis and infectious agents?: A systematic review and meta-analysis. BMC Pulm Med. 2016;16(1):1–13. doi:10.1186/s12890-016-0332-z. [PubMed: 26728359]
48. Fang C, Huang H, Xu Z. Immunological evidence for the role of mycobacteria in sarcoidosis: A meta-analysis. PLoS One. 2016;11(8):1–14. doi:10.1371/journal.pone.0154716.
49. Tanabe T, Ishige I, Suzuki Y, et al. Sarcoidosis and NOD1 variation with impaired recognition of intracellular Propionibacterium acnes. Biochim Biophys Acta - Mol Basis Dis. 2006;1762(9):794–801. doi:10.1016/j.bbadis.2006.07.006.
50. Becker ML, Martin TM, Doyle TM, Rosé CD. Interstitial pneumonitis in Blau syndrome with documented mutation in CARD15. Arthritis Rheum. 2007;56(4):1292–1294. doi:10.1002/art.22509. [PubMed: 17393391]
51. Chauhan K, Michet C. A Case of Blau Syndrome. Case Rep Rheumatol. 2014;2014:1–3. doi:10.1155/2014/216056.
52. Ellis JC, Faber BG, Uri IF, Emerson JS. Early onset sarcoidosis (Blau syndrome): Erosive and often misdiagnosed. Rheumatol (United Kingdom). 2020;59(5):1179–1180. doi:10.1093/rheumatology/kez484.

53. Jha S, Mittal S, Kumar RR, Dhooria A, Rawat A, Dhir V. An unusual cause of deforming erosive arthritis in an adult. Rheumatol (United Kingdom). 2020;59(3):602. doi:10.1093/rheumatology/kez312.
54. Poline J, Bourrat E, Meinzer U. Camptodactlyly in Pediatric Practice: Blau Syndrome. J Pediatr. 2020;221(June):257–259. doi:10.1016/j.jpeds.2020.01.057. [PubMed: 32113659]
55. Visser H, Vos K, Zanelli E, et al. Sarcoid arthritis: clinical characteristics, diagnostic aspects, and risk factors. Ann Rheum Dis. 2002;61:499–504. doi:10.1136/ard.61.6.499. [PubMed: 12006321]
56. Ungprasert P, Wetter DA, Crowson CS, Matteson EL. Epidemiology of Cutaneous Sarcoidosis, 1976–2013: A Population Based Study From Olmsted County, Minnesota. J Eur Acad Dermatol Venereol. 2016;30(10):1799–1804. doi:10.1111/jdv.13760.Epidemiology. [PubMed: 27324138]
57. Jindal AK, Pilania RK, Suri D, et al. A young female with early onset arthritis, uveitis, hepatic, and renal granulomas: a clinical tryst with Blau syndrome over 20 years and case-based review. Rheumatol Int. 2019;(0123456789):1–9. doi:10.1007/s00296-019-04316-6.
58. Turk MA, Hayworth JL, Nevskaya T, Pope JE. Ocular manifestations in rheumatoid arthritis, connective tissue disease, and vasculitis: a systematic review and meta-analysis. J Rheumatol. 2020:1–25. doi:10.3899/jrheum.190768. [PubMed: 31894089]
59. Jabs DA, Houk JL, Bias WB, Arnett FC. Familial granulomatous synovitis, uveitis, and cranial neuropathies. Am J Med. 1985;78(5):801–804. doi:10.1016/0002-9343(85)90286-4. [PubMed: 3993660]
60. Khubchandani R, Hasija R, Touitou I, Khemani C. Aortoarteritis and cardiomyopathy in a child with Blau Syndrome. Pediatr Rheumatol. 2011;9(S1):1–2. doi:10.1186/1546-0096-9-s1-p36.
61. Khubchandani RP, Hasija R, Touitou I, Khemani C, Wouters CH, Rose CD. Blau arteritis resembling Takayasu disease with a novel NOD2 mutation. J Rheumatol. 2012;39(9):1888–1892. doi:10.3899/jrheum.120156. [PubMed: 22859352]
62. Whyte MP, Lim E, McAlister WH, et al. Unique Variant of NOD2 Pediatric Granulomatous Arthritis With Severe 1,25-Dihydroxyvitamin D-Mediated Hypercalcemia and Generalized Osteosclerosis. J Bone Miner Res. 2018;33(11):2071–2080. doi:10.1002/jbmr.3532. [PubMed: 29933504]
63. Milman N, Hoffmann AL, Byg KE. Sarcoidosis in children. Epidemiology in Danes, clinical features, diagnosis, treatment and prognosis. Acta Paediatr. 1998;87(8):871–878. doi:10.1080/080352598750013662. [PubMed: 9736236]
64. Nia AE, Nabavi M, Nasab MM, Kashef S. Central Nervous System Involvement in Blau Syndrome: A New Feature of the Syndrome? J Rheumatol. 2007;34:2504–2505. doi:10.1186/1546-0096-12-33. [PubMed: 18061972]
65. Weiler V, Redtenbacher S, Bancher C, Fischer MB, Smolen JS. Concurrence of sarcoidosis and aortitis: Case report and review of the literature. Ann Rheum Dis. 2000;59(11):850–853. doi:10.1136/ard.59.11.850. [PubMed: 11053059]
66. Izumikawa K, Motoi N, Takaya H, et al. A case of concurrent sarcoidosis, aortitis syndrome and Crohn's disease. Intern Med. 2011;50(23):2915–2917. doi:10.2169/internalmedicine.50.5298. [PubMed: 22129508]
67. Liu Y, Li S, Cao J, et al. Concurrence of sarcoidosis and Takayasu aortitis. Chin Med J (Engl). 2015;128(6):851–852. doi:10.4103/0366-6999.152694. [PubMed: 25758287]
68. Saha BK, Burns SL, Foulke LA, Judson MA. Coexistent Takayasu arteritis and sarcoidosis: A case report and review of the literature. Sarcoidosis Vasc Diffus Lung Dis. 2019;36(4):311–317. doi:10.36141/svdld.v36i4.8667.
69. Nocton JJ, Stork JE, Jacobs G, Newman AJ. Sarcoidosis associated with nephrocalcinosis in young children. J Pediatr. 1992;121(6):937–940. doi:10.1016/S0022-3476(05)80347-6. [PubMed: 1447662]
70. Rodriguez GE, Shin BC, Abernathy RS, Kendig ELJ. Serum angiotensin-converting enzyme activity in normal children and in those with sarcoidosis. J Pediatr. 1981;99(1):68–72. doi:10.1016/s0022-3476(81)80959-6. [PubMed: 6265617]
71. Bénéteau-Burnat B, Baudin B, Morgant G, Baumann FC, Giboudeau J. Serum angiotensin-converting enzyme in healthy and sarcoidotic children: comparison with the reference interval for adults. Clin Chem. 1990;36(2):344–346. doi: 10.1093/clinchem/36.2/344. [PubMed: 2154343]

72. Niederer RL, Al-Janabi A, Lightman SL, Tomkins-Netzer O. Serum Angiotensin-Converting Enzyme Has a High Negative Predictive Value in the Investigation for Systemic Sarcoidosis. Am J Ophthalmol. 2018;194:82–87. doi:10.1016/j.ajo.2018.07.010. [PubMed: 30053466]
73. Ungprasert P, Carmona EM, Crowson CS, Matteson EL. Diagnostic Utility of Angiotensin Converting Enzyme in Sarcoidosis: A Population-Based Study. Lung. 2016;195(1):91–95. doi:10.1016/j.physbeh.2017.03.040.
74. Eurelings LEM, Miedema JR, Dalm VASH, et al. Sensitivity and specificity of serum soluble interleukin-2 receptor for diagnosing sarcoidosis in a population of patients suspected of sarcoidosis. PLoS One. 2019;14(10):1–15. doi:10.1371/journal.pone.0223897.
75. Simonini G, Xu Z, Caputo R, et al. Clinical and transcriptional response to the long-acting interleukin-1 blocker canakinumab in Blau syndrome-related uveitis. Arthritis Rheumatol. 2013;65(2):513–518.
76. Achille M, Ilaria P, Teresa G, et al. Successful treatment with adalimumab for severe multifocal choroiditis and panuveitis in presumed (early-onset) ocular sarcoidosis. Int Ophthalmol. 2016;36(1):129–135. doi:10.1007/s10792-015-0135-x. [PubMed: 26449230]
77. Arvesen KB, Herlin T, Larsen DA, et al. Diagnosis and treatment of blau syndrome/early-onset sarcoidosis, an autoinflammatory granulomatous disease, in an infant. Acta Derm Venereol. 2017;97(1):126–127. doi:10.2340/00015555-2485. [PubMed: 27304707]
78. Nagakura T, Wakiguchi H, Kubota T, et al. Tumor necrosis factor inhibitors provide longterm clinical benefits in pediatric and young adult patients with Blau Syndrome. J Rheumatol. 2017;44(4):536–538. [PubMed: 28604349]
79. Thareja S, Kollmann K, Ardalan K, Klein-Gitelman MS, Paller AS, Arkin LM. Oral macrolides for the dermatologic manifestations of Blau syndrome. JAMA Dermatology. 2017;153(10):1066–1067. doi:10.1001/jamadermatol.2017.2172. [PubMed: 28724114]
80. Lu L, Shen M, Jiang D, et al. Blau syndrome with good Reponses to Tocilizumab: A case report and focused literature review. Semin Arthritis Rheum. 2018;47(5):727–731. doi:10.1016/j.semarthrit.2017.09.010. [PubMed: 29110911]
81. Naik AU, Annamalai R, Biswas J. Uveitis in sporadic Blau syndrome: Long-term follow-up of a refractory case treated successfully with adalimumab. Indian J Ophthalmol. 2018;66(10):1483–1485. doi:10.4103/ijo.IJO_629_18. [PubMed: 30249847]
82. Millington GWM, Dobson J, Holden S, et al. Sporadic Blau syndrome treated with adalimumab. Clin Exp Dermatol. 2019;44(7):811–813. doi:10.1111/ced.14016. [PubMed: 31232485]
83. Martin TM, Zhang Z, Kurz P, et al. The NOD2 defect in Blau syndrome does not result in excess interleukin-1 activity. Arthritis Rheum. 2009;60(2):611–618. doi:10.1002/art.24222. [PubMed: 19180500]
84. Reese T, Villegas L, Wood J, Gotte A. A 21-Month-Old Male With Refusal to Walk, Rash, and Weight Loss. Arthritis Care Res. 2017;69(2):286–293. doi:10.1002/acr.22792.
85. Toral-López J, González-Huerta LM, Martín-del Campo M, Messina-Baas O, Cuevas-Covarrubias SA. Familial Blau syndrome without uveitis caused by a novel mutation in the nucleotide-binding oligomerization domain-containing protein 2 gene with good response to infliximab. Pediatr Dermatol. 2018;35(3):e180–e183. doi:10.1111/pde.13475. [PubMed: 29570830]
86. Paç Kisaarslan A, Sözeri B, Şahin N, et al. Blau syndrome and early-onset sarcoidosis: A six case series and review of the literature. Arch Rheumatol. 2020;35(1):111–127. doi:10.5606/ArchRheumatol.2020.7060.
87. Mezouar S, Diarra I, Roudier J, Desnues B, Mege JL. Tumor necrosis factor-alpha antagonist interferes with the formation of granulomatous multinucleated giant cells: New insights into Mycobacterium tuberculosis infection. Front Immunol. 2019;10(AUG):1–14. doi:10.3389/fimmu.2019.01947. [PubMed: 30723466]
88. Baughman RP, Nagai S, Balter M, et al. Defining the clinical outcome status (COS) in sarcoidosis: Results of WASOG Task Force. Sarcoidosis Vasc Diffus Lung Dis. 2011;28(1):56–64.
89. Johns CJ, Michele TM. The clinical management of sarcoidosis. A 50-year experience at the Johns Hopkins Hospital. Medicine (Baltimore). 1999;78(2):65–111. doi:10.1097/00005792-199903000-00001. [PubMed: 10195091]

90. Baughman RP, Lower EE. Treatment of Sarcoidosis. Clin Rev Allergy Immunol. 2015;49(1):79–92. doi:10.1007/s12016-015-8492-9. [PubMed: 25989728]