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Blau syndrome associated with a Novel NOD2 mutation

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Abstract

Blau syndrome is a rare, genetic, systemic autoinflammatory disease that presents in early childhood with granulomatous dermatitis, inflammatory arthritis, and uveitis. Blau syndrome follows an autosomal dominant inheritance pattern and is typically caused by a gain of function mutation in the NOD2/CARD15 gene. NOD2/CARD15 normally activates nuclear factor-kappa B and other genes controlling innate immune and inflammatory responses and is associated with several autoinflammatory conditions, including allergic diseases, Crohn's disease, and Early Onset Sarcoidosis. While some mutations associated with Blau syndrome have been identified, the full spectrum of mutations hasn't been described. Thus, we present a case of Blau syndrome in a 40-year-old male caused by a novel, a heterozygous mutation in the NOD2 gene [variant c.1144G>A (p.Asp382Asn)].

Keywords

blau Syndrome; nod2 mutation; genetic testing; granulomatous dermatitis.

Introduction

Blau syndrome is a rare, genetic, systemic autoinflammatory disease that presents in early childhood with granulomatous dermatitis, inflammatory arthritis, and uveitis [1]. Patients typically present with skin and joint findings and later develop ocular symptoms as the disease progresses [2]. Blau syndrome follows an autosomal dominant inheritance pattern and is typically caused by a gain of function mutation in the NOD2/CARD15 gene [3,4]. The NOD2/CARD15 gene controls caspase activation and recruitment, which is involved in programmed cell apoptosis and immune function [2,5]. NOD2/CARD15 mutations are associated with several autoinflammatory conditions, including allergic diseases, Crohn's disease, and Early Onset Sarcoidosis [6,7].

NOD2/CARD15 normally activates nuclear factor-kappa B and other genes controlling innate immune and inflammatory responses [4]. Nuclear factor-kappa B is mostly expressed in monocytes, granulocytes, and dendritic cells, major components of granulomatous inflammation, and gain-of-function mutations in NOD2/CARD15 can cause increased signaling via these pathways, resulting in the inflammatory symptoms associated with Blau syndrome [8,9]. While some mutations associated with Blau syndrome have been identified, the full spectrum of mutations hasn'tbeen described. We present a case of Blau syndromecaused by a novel, heterozygous mutation of NOD2.

Case Report

Our case presents a 40-year-old male with Blau syndrome who was seen in the rheumatology clinic for clinical management. The patient initially presented with widespread dermatitis in his early childhood. He was suspected to have sarcoidosis at that time, but the differential remained broad, and subsequent skin biopsies were nonspecific. His symptoms improved with sunlight exposure, and his diffuse rash resolved entirely by his early teens. However, soon after the dermatitis resolved, he developed uveitis of the right eye. He was evaluated at a major academic medical center and found to have no evidence of sarcoidosis or other systemic rheumatic disease. His symptoms further progressed to low back, bilateral hip, knee, and ankle inflammatory arthritis. His sister also developed similar symptoms. With the triad of dermatitis, uveitis, and inflammatory arthritis, the seronegative workup, and a familial component, he was clinically diagnosed with Blau syndrome.

At the time when his treatment was started, he had difficulty ambulating and required an assistive walking device. His initial treatment included a regimen of corticosteroids, methotrexate, and infliximab. He showed significant improvement and was able to regain full physical functionality with a corticosteroid-free maintenance regimen of methotrexate and infliximab.

Given the hereditary nature of Blau syndrome, the patient and his sister underwent comprehensive genetic testing. Both of their genetic testing revealed a heterozygous mutation in the NOD2 gene [variant c.1144G>A (p.Asp382Asn)]. Further genetic testing is pending to determine if the mutation was inherited by the children of the patient's sister.

Discussion

This case demonstrates an atypical, novel gene mutation carried by a patient with Blau syndrome. The patient's clinical presentation, identified mutation in NOD2/CARD15, and his sister's diagnosis of Blau syndrome with an identical variant on genetic testing, support this novel mechanism of inheritance. A review of the literature identified a limited number of cases identifying novel, heterozygous mutation variants associated with Blau syndrome. A review of Blau syndrome in 2012 found 193 documented cases of the disease associated with 11 unique mutations of the NOD2/CARD15 gene [2]. Multiple case reports identifying novel mutations have been published since that time, including a case series identifying 6 novel NOD2/CARD15 mutations in 2020,but the Asp382Asn variant has previously not been described in association with Blau syndrome [10].

In addition, this case exemplifies the importance and advantages of genetic testing in cases of Blau

syndrome. Blau syndrome follows an autosomal dominant inheritance pattern, which increases the likelihood of the disease to propagate through generations [1,6]. In our case, the patient and his sister both wanted to obtain genetic testing in order to assess the possibility of inheritance of Blau syndrome in his sister's children. Early identification and treatment of Blau syndrome is key, as symptoms can progress to severe joint contractures and blindness if the disease is left untreated [11]. In addition, atypical cases of Blau syndrome have been associated with cardiovascular, renal, and neurological manifestations, which further warrant observation from the treating physician [6]. Thus, genetic testing can be beneficial in identifying specific mutations that are inherited in families and determining the risk that family members have of manifesting the disease. Early detection leads to early appropriate treatment of the disease.

It is recommended that treatment for Blau syndrome begin with a regimen of corticosteroids and methotrexate [12]. In the event of incomplete control with a corticosteroid and methotrexate alone, a biologic may be added to the treatment plan. Numerous cases have demonstrated the efficacy of infliximab in treating Blau syndrome, with many patients achieving complete remission of all symptoms [13,14]. For patients unresponsive to infliximab, tocilizumab may be considered as a potential replacement biologic [15]. The treatment of Blau syndrome can be difficult, but in this case, the combination of corticosteroids, methotrexate, and infliximab were sufficient to control the patient's initial clinical symptoms.

While the association of NOD2/CARD15 mutations and Blau syndrome has been established, the mechanism underlying the disease process and the full spectrum of mutations that can precipitate the condition remain incompletely understood, and further investigation is being undertaken.

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