Blau Syndrome

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Core Messages

- Although Blau syndrome is rare, it is more common than previously believed.
- Knowledge of the biological effects caused by the mutations that result in Blau syndrome has the potential to clarify the pathogenesis of more common forms of uveitis.

77.1 Definition

Blau syndrome is an autosomal dominant disease which characteristically results in a granulomatous rash, arthritis, and uveitis. Blau syndrome was first described in 1985 in two separate reports [3, 7]. Although the description by Jabs and colleagues appeared first, the eponym, Blau, is widely applied to this syndrome. Many prefer the term, "pediatric granulomatous arthritis and uveitis" to the name "Blau" [15].

77.2 Clinical Manifestations

77.2.1 General Disease

The triad of skin, joint, and eye disease is most characteristic. Most patients develop a tan-colored rash before the age of 5. The joint disease often affects the wrists and fingers. A "telescoped" appearance to the finger is referred to as camptodactyly.

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Other organs that have been involved include the cranial nerves, lung, and large arteries [2, 18]. In contrast to sarcoidosis, the lung is not characteristically involved in Blau syndrome.

Patients with Blau syndrome have widespread inflammation but no detectable autoantibodies. Consequently Blau syndrome is designated as being autoinflammatory to distinguish it from autoimmune diseases.

77.2.2 Ocular Disease

The uveitis is variable but generally it is bilateral and associated with chorioretinal scarring. Cataract and glaucoma are common complications. Often the visual loss is severe [9].

77.3 Etiology and Pathophysiology

Blau syndrome results from a single base pair mutation in a gene known variously as NOD2 or CARD15 [11]. This gene codes for a protein with three distinct domains: an amino terminal pair of caspase recruitment domains (CARDs), a central nucleotide-binding domain (also called a nucleotide oligomerization domain or NOD), and carboxyl terminal leucine-rich repeats. All of the mutations associated with Blau have been located in or very near the nucleotide-binding domain. To date, all of these mutations have complete penetrance, meaning that no one has been identified with one of the known mutations and an absence of inflammatory disease. The NOD2 gene also has recognized polymorphisms in the domain that codes for the leucine-rich repeats and which have been associated with increased susceptibility to Crohn's disease [6]. Most patients who had been previously diagnosed as having early-onset sarcoidosis also have a mutation in the NOD2 nucleotide-binding domain even if there is no family history of a similar disease [14].

Understanding the function of the Nod2 protein will obviously clarify the pathogenesis of Blau syndrome. It is clear that the Nod2 protein acts as a sensor for muramyl dipeptide [17] which is a ubiquitous component of bacterial cell walls. Leucine-rich repeats are also present in TLR receptors. TLRs are cell surface proteins that recognize microbial products such as endotoxin, flagellin, RNA, and DNA. TLRs are a vital component of the innate immune response. The biological consequences that result from the mutations associated with Blau are not clearly understood. Nod2 has roles in activating intracellular kinases including RIP2 [13] and MAP kinase; it activates the critical transcription factor, NF-kB; it activates caspases resulting in apoptosis; and it activates the inflammasome [10], a group of proteins that regulate the synthesis of several cytokines including interleukin-1 beta. Despite all that is known about the function of Nod2, the biological consequences of the mutations in Nod2 are less completely understood.

A trio of autoinflammatory diseases known as Muckle-Wells syndrome, familial cold urticaria syndrome, and neonatal-onset multisystem inflammatory disease (NOMID) occurs secondary to a mutation in a protein called cryopyrin [5, 8] (see Chap. 78). The gene for this protein has a homologous structure to Nod2. Cryopyrin is an essential component of the inflammasome that controls NOD2 synthesis. Understanding the function of cryopyrin has led to the successful treatment of these diseases with inhibitors of interleukin-1 [4]. In addition, this research has shed light on the role of the inflammasome in much more common forms of inflammation, namely, gout [16]. Consequently it seems logical that similar insights can derive from studies on Nod2 and the mutations leading to Blau syndrome.

77.4 Diagnosis

A diagnosis of Blau syndrome can generally be made reliably if the classic clinical triad is present during childhood, and there is a family history of a similar disease. The detection of noncaseating granulomas as in a skin biopsy is very helpful in supporting the diagnosis. An international consortium is available to validate the diagnosis by testing for known mutations in the NOD2 gene [15].

77.5 Differential Diagnosis

Blau syndrome is most often confused with sarcoidosis which rarely begins in childhood and which almost always involves the lung and lymph node. However, children with sarcoidosis may also have joint involvement as is common in Blau syndrome. Several studies have now concluded that many patients previously diagnosed with early-onset sarcoidosis actually have de novo mutations in the NOD2 gene [14, 15]. The international consortium studying Blau syndrome has also described other granulomatous syndromes in childhood such as one that commonly causes panniculitis.

77.6 Treatment

Corticosteroids, topical or systemic, are presently the most effective therapy for Blau syndrome. Although inhibitors of tumor necrosis factor or interleukin-1 have been tried with some success, the authors have been disappointed with either approach [1, 12].

77.7 Prognosis

The severity of the disease varies and is presumably influenced by environmental and epigenetic effects. The eye disease is potentially blinding.

Take-Home Pearls

- Many patients previously diagnosed as having early-onset sarcoidosis actually suffer from Blau syndrome.
- Although it is extremely rare, the mutations responsible for Blau syndrome could contribute to an understanding of intraocular inflammation.

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