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Blau Syndrome: subepithelial infiltrates as uncommon ophthalmologic manifestation

Síndrome de Blau: infiltrados subepiteliais como manifestações oftalmológicas incomuns

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Abstract

The Blau syndrome is an autosomal dominant hereditary disease which can also occur sporadically via "de novo" mutation. Overall it has early onset and its classic triad includes arthritis, dermatitis and uveitis. This paper describes clinical and mainly especially ophthalmologic manifestations of a patient diagnosed with Blau syndrome with emphasis on an uncommon finding of corneal subepithelial infiltrates, rarely described in the literature.

Keywords: *Uveitis/etiology; Uveitis/genetics; Cornea; Arthritis/genetics; Dermatitis/genetics; Child*

Resumo

A Síndrome de Blau é uma doença de caráter hereditário autossômico dominante a qual também pode ocorrer de forma esporádica via mutação "de novo". Em geral, tem aparecimento precoce ainda na primeira infância e sua tríade clássica inclui artrite, dermatite e uveíte. Este trabalho visa relatar as manifestações clínicas e principalmente oftalmológicas de uma paciente diagnosticada com Síndrome de Blau com ênfase ao achado incomum de infiltrados corneanos subepiteliais, raramente descrito na literatura.

Descritores: Uveíte/etiologia; Uveíte/genética; Córnea; Artrite/genética; Mutação; Dermatite/genética; Criança

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Introduction

Blau Syndrome is an inherited autosomal dominant condition occuring in 50-90% of cases by mutation "de novo".[1] The manifestation of the syndrome may be early, and present a classic triad including arthritis, dermatitis and uveitis.[2]

In 1985, Blau et al. described a new syndrome characterized by arthritis, anterior uveitis, and cutaneous rash of variable intensity and onset in 11 members of the same family distributed over 4 generations.[3] Similar findings have also been described by Jabs et al. almost simultaneously.[4] In 1989, Pastores et al. described 3 cases characterized as familial juvenile systemic granulomatosis.[5] Signs and symptoms begin in childhood, usually before 4 years of age, and there may be granulomatous dermatitis which is usually the first sign of Blau Syndrome, arthritis, and uveitis. Subsequently, with the identification of the disease-causing mutation in NOD2 [6,7] a new line of research was started, and it was possible to see that the pathology can be both familial and sporadic.[8] The diagnosis is made through the conjugation of clinic and family history, histological detection and laboratory investigation. This report describes the case of corneal subepithelial infiltrates on biomicroscopy, a rare ocular finding in this syndrome.

Case Report

VVF, 13 years old, female, presented at 2 months of age exanthema on the face, limbs and flanks, progressively evolving with arthritis of the hands and wrists. At age 3, she was referred for ophthalmologic examination complaining of ocular hyperemia and tearing. The exam revealed anterior uveitis in both eyes (BE) with no other risk alteration. Laboratory tests revealed increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); positive rheumatoid factor (RF), and negative antinuclear factor (ANF). For diagnostic elucidation, a skin biopsy was carried out showing the presence of multiple granulomas in the dermis without signs of necrosis. The genetic test revealed the presence of R334W mutation. Parents were also tested for mutation with negative result. The patient was treated with prednisone, naproxen and methotrexate, and the ophthalmologic treatment included the use of eyedrops of prednisolone acetate 1.0% and tropicamide 1.0%, with good control of systemic and ocular manifestations. One year later, she presented recurrence of systemic and ocular symptoms, and infliximab was used with good results. The patient is asymptomatic in the use of infliximab, methotrexate and folic acid. Ophthalmologic examination revealed visual acuity equal to 20/20 in BE, biomicroscopy revealed absence of inflammatory reaction, ovoid subepithelial infiltrates in BE (Figures 1 and 2), posterior synechia in the left eye (Figure 2), and fundoscopy revealed normal exam in BE.

Discussion

Blau syndrome is a disease of dominant autosomal hereditary character when familial; however, it can occur sporadically by mutation "de novo".[7] Its prevalence remains unknown, since many cases are not diagnosed or are considered as other inflammatory diseases. Symptoms usually start before the age of four, and are related to a mutation in the gene NOD2.[9]

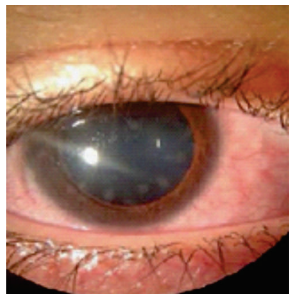

Figure 1: Subepithelial infiltrates

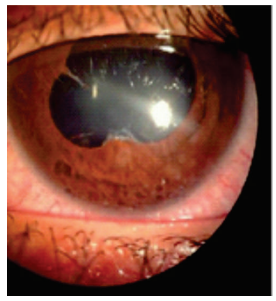

Figure 2: Posterior synechiae

Most mutations related to Blau Syndrome reported to date are at or near the domain NOD / NACHT of binding the nucleotide to protein NOD2, although it may also be found in the C-terminal region characterized by a replication structure rich in leucine. Over the past few years, there was an increase in the number of different mutations NOD2 associated with Blau, and new mutations NOD2 are still cataloged regularly.[10-15] In the present report, the patient presented the mutation R334W which is related to gene NOD2, being this mutation responsible for 50-90% of patients presenting the classic Blau syndrome triad.

The disease is characterized by a classic triad including granulomatous dermatitis, arthritis and uveitis. Cutaneous lesions usually appear within the first year of life, and the spectrum may range from simple rash to asymptomatic nodules or papules. Early signs of arthritis occur between 2 and 4 years of age, and typically affect peripheral joints especially in the wrists, knees, ankles, and proximal interphalangeal joints of the hands. Tenosynovitis is also a characteristic, as is the presence of joint edema.[16] Other significant signs in the osteoarticular examination are synovial cysts and camptodactyly.[5]

About 80% of patients developed ocular disease with an average onset at 4 years of age.[9] Uveitis may present as granulomatous anterior uveitis with potential evolution to severe panuveitis with multifocal choroiditis, usually bilateral and frequently associated with severe visual loss. In these cases, vitreous inflammation is common and may remain persistently active for years.[17] Ophthalmologic manifestations were well determined by the study by Latkany et al.,[18] who reviewed 16 patients from 8 families with juvenile systemic granulomatosis. Of these, 14 patients presented panuveitis with multifocal choroiditis. One patient had only anterior uveitis. One patient presented panuveitis and ischemic optic neuropathy probably secondary to vasculitis. Cataract, glaucoma, band keratopathy, cystoid macular edema, and optic disc edema were described. All patients had polyarthritis, and at least 9 had skin rashes. In the present report, anterior uveitis with bilateral corneal involvement was described, with no posterior segment manifestations nor secondary ophthalmologic complications.

Other systemic alterations present in patients with Blau Syndrome include fever, lymphadenopathy, erythema nodosum, leukocytoclastic vasculitis, transient neuropathies, granulomatous glomerular interstitial nephritis with potential evolution to chronic renal failure, hypertension, pericarditis, and hepatic granulomas.[19] In the present report, the patient presented cutaneous, ophthalmologic and osteoarticular disease without other systemic alterations.

Common laboratory alterations include hypercalcemia, hypercalciuria, increased angiotensin converting enzyme (ACE)

and HSV, leukopenia, proteinuria, hematuria, and pyuria. The liver function tests may be altered and the rheumatoid factor RF is generally positive.[9] Laboratory alterations were found in the present report.

Histopathological exams reveal granulomatous inflammation in the dermis containing epithelioid cells and occasionally Langerhans cells. The presence of lymphomononuclear infiltrate is frequent, and no case showed the presence of necrosis.[20]

The diagnosis is clinical from the identification of the classical triad and associated symptoms. Skin biopsy should be carried out in a complementary manner, considering that the skin offered better diagnostic capacity when compared to synovium, with confirmatory histology in more than 90% of patients suspected of Blau Syndrome,[9] as in the present report.

Systemic treatment involves the use of systemic corticosteroids in variable doses, which should be used carefully since the side effects of prolonged use represent great morbidity to the patients.[21] Im case control of the disease requires prolonged use of corticosteroids or the patient presents adverse events to this treatment, it is mandatory to initiate the use of immunosuppressants such as methotrexate and anti-tumor necrosis factor biological agents may be used together or separately, in order to obtain adequate control of the syndrome. Uveitis should be treated according to the anatomical classification and degree of inflammation.[21]

Patients with Blau Syndrome rarely have subepithelial corneal infiltrates, as in the case described according to the literature available to date. When present, these infiltrates are characteristically ovoid, and they do not cause visual repercussion unless they obstruct the visual axis.[7]

The present report contributes to the description of unusual ophthalmological manifestations of Blau Syndrome since ovoid corneal infiltrates are rarely observed.

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