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Simultaneous presentation of idiopathic uveitis in monozygotic 4-year-old twin boys

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ABSTRACT

Purpose: To report monozygotic twin 4-year-old boys with chronic bilateral anterior uveitis with simultaneous onset.

Observations: Here we report monozygotic twin 4-year-old boys with chronic bilateral anterior uveitis. The boys had simultaneous onset of uveitis and identical features. Evaluation, including whole exome sequencing (WES), failed to reveal a specific causative etiology. Each patient responded well to immune modulation and achieved uveitis remission on methotrexate monotherapy off topical glucocorticoids.

Conclusions and Importance: From this case of monozygotic twin boys presenting with chronic uveitis, we conclude that monozygotic twins may warrant evaluation in the setting of idiopathic uveitis, especially in young patients unable to express an adequate history.

1. Introduction

Uveitis affects approximately three in 100,000 children.[1] Pediatric uveitis is usually noninfectious. Uveitis associated with juvenile idiopathic arthritis is the most recognized form of pediatric uveitis, although other conditions such as tubulointerstitial nephritis and uveitis (TINU) syndrome, intermediate uveitis, and chronic idiopathic uveitis present in the pediatric population. Diagnosis of juvenile uveitis is often delayed due to lack of reported symptoms or visible signs of disease. Therefore, children are typically screened for uveitis only if they have a clear complaint or a related condition, including juvenile idiopathic arthritis.[2]

2. Case report

Twin white 4-year-old males presented to pediatric rheumatology for evaluation and treatment of bilateral uveitis diagnosed the same month. On history, boy A and boy B developed an erythematous, but non-painful sclera, lasting for about one week associated with nasal congestion and rhinorrhea four months before ophthalmic presentation. Their parents attributed these symptoms to a viral illness. They did not seek medical care and symptoms resolved without intervention. Following this episode, boy A gradually developed difficulty seeing pictures and letters in books being read to him. Frequent mild scleral erythema occurred without discomfort. Four months following the initial episode of scleral injection, he presented to an ophthalmologist and was found to have visual acuity of 20/60 OD and 20/70 OS with Allen pictures, multiple posterior synechiae and anterior uveitis with 2+ anterior chamber cell and flare and small subcapsular cataracts. Posterior segment exam was unremarkable.

Boy B remained asymptomatic after his initial episode of scleral injection and upper respiratory symptoms. His parents did not note changes in visual behavior like his brother. After Boy A was found to uveitis, it was recommended that boy B undergo a slit-lamp exam as a precaution. Boy B was noted to have visual acuity of 20/50 OU, asymptomatic bilateral anterior uveitis, with 3+ anterior chamber cells in both eyes with flare, multiple synechiae, and trace subcapsular cataracts.

The twins had no significant past medical history, surgical history, or environmental history. They were the result of a full-term uncomplicated pregnancy. They were not using prescription medications and were up to date on all recommended vaccines. The family history was unremarkable, with no significant ocular or autoimmune disease. The

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twin boys have an older half-sister who is healthy.

A thorough review of systems was otherwise negative. Labs for both patients were notable for negative ANA, ANCA, ACE, lysozyme, Bartonella titers, HLA-B27, normal urinalysis, and normal beta-2-microglobulin. They did not live or visit a Lyme endemic region. Sequencing did not uncover a clear causal variant: whole genome sequencing with read depth >30x for both twins and their parents revealed no potentially damaging variants consistent with either autosomal recessive inheritance or occurrence of *de novo* events. Sequencing did reveal a *de novo* deletion of 1526bp at chr7:17,575,850 (hg19); this region was more than 100kb from any coding gene associated with uveitis. Sequencing and bioinformatics analysis was performed as previously described.[3] Attention was paid both to diseases of immune dysregulation and autoimmunity, and diseases known to cause uveitis. Specifically, no mutations in NOD2/CARD15, associated with Blau-Jabs syndrome, or coding mutations in BTK, associated with juvenile idiopathic arthritis, were identified.

Boy A was started on topical prednisolone acetate three times daily by the community ophthalmologist at diagnosis. He was referred to pediatric ophthalmology, and the prednisolone was increased for continued ocular inflammation. Topical atropine was initiated for his synechiae.

Boy B was started on prednisolone acetate drops three times a day and atropine three times a week. The twins were referred to pediatric rheumatology. They lacked signs of a systemic autoimmune process on physical examination and had an unremarkable laboratory workup as detailed above. Despite two months of topical prednisolone acetate drops, both boys had persistent inflammation: while both were on three times daily prednisolone drops, Boy A had 1+ cells and Boy B had 2+ cells with trace flare. Both boys still had multiple small synechiae not broken by cycloplegia. Methotrexate 20 mg weekly was initiated in the boys two-and-a-half months after their initial ophthalmologic evaluation. They both remained on varying doses of topical prednisolone and atropine for the next seven months for ongoing inflammation and synechiae. Eventually the twins were able to discontinue topical therapy at the same time and remain in remission on methotrexate monotherapy two years after presentation. At last visit, thirty-eight months after initial presentation, corrected visual acuity was 20/20 OD and 20/30 OS for Boy A and 20/30 OU for Boy B. Both had quiet anterior segments. Considering their age at presentation and improvement in visual acuity with systemic treatment, optical coherence tomography (OCT) to screen for cystoid macular edema was not performed.

3. Discussion

We describe an interesting report of simultaneous onset chronic idiopathic anterior uveitis affecting monozygotic twins. Isolated reports of uveitis occurring in monozygotic twins exist in the setting of intermediate uveitis[4], neovascular inflammatory vitreoretinopathy[5], Blau-Jabs syndrome[6], TINU[7], and Vogt-Koyanagi-Harada syndrome.[8] However, these patients have idiopathic onset which adds to our understanding of disease pathogenesis. The patients presented here underwent unremarkable extensive rheumatologic, infectious, and ophthalmologic workup, as well as whole-genome trio sequencing (sequencing of the boys alongside their parents, in order to identify *de novo* or compound heterozygous mutations). Serologies excluded common infectious causes of uveitis.

We believe that their disease is likely an isolated autoimmune idiopathic uveitis based on their history, physical examination, and negative serologic workup. We cannot rule out, though, that their uveitis was caused by an environmental exposure or infection, either *in utero* or in their shared environment. Both boys had an antecedent illness, presumed to be viral by their parents, with conjunctival and scleral injection alongside upper respiratory symptoms. This illness occurred four months prior to the recognition of their uveitis, and there was no clear serologic evidence of infections that commonly cause pediatric uveitis such as *Bartonella*. It would also be unusual for infection to manifest with identical clinical features in both boys.[9] Acute uveitis is also a rare, but known, complication of more common viral illnesses, such as coxsackie virus. However, coxsackie uveitis is typically unilateral and posterior[10], as is typically the case for other infectious processes such as toxoplasmosis or toxocariasis. The presence of bilateral anterior segment ocular disease in both boys makes an uncommon infectious etiology less likely.

The simultaneous onset in monozygotic twins strongly suggests the possibility of genetic predisposition, however, none was found on exome or genome analysis (performed under research protocol) of the boys and their parents. It possible this predisposition along with the preceding infection resulted in a loss of tolerance triggering the uveitis. Such a mechanism is postulated with specific HLA class II alleles increasing susceptibility for Vogt-Koyanagi-Harada syndrome and associated uveitis[11]. There are several genes associated with uveitis, but they are predominately also associated with co-occurring symptoms or dysmorphology. For example, Blau-Jabs syndrome (juvenile systemic granulomatosis, caused by NOD2 mutations) manifests with granulomatous ocular, cutaneous, and articular disease; and X-linked lymphoproliferative syndrome type 2 (BIRC4 mutation) with hemophagocytic lymphocytic histiocytosis and uveitis.[12] The lack of a clear causal variant on trio WES does not exclude a genetic etiology, especially given the rapidly expanding pool of recognized immune disorders. Further, it is possible a causative mutation may reside in a non-coding region undetected by WES. We have recommended the family undergo reconsideration for genetic etiologies in the future, especially if the boys' uveitis persists.

Parents and patients commonly ask their physician whether a sibling, child, or other relative is at risk of disease. In some diseases, we have established the risk to monozygotic twins; for instance, in systemic lupus the concordance is 11%, and in type I diabetes mellitus the concordance is 26.[13] The concordance risk for juvenile idiopathic uveitis is not well established.

4. Conclusions

Indications to evaluate for uveitis in pediatrics poses a unique challenge because patients are rarely adequate historians and can be asymptomatic. This case provides support for shared genetic predisposition in monozygotic twins. It is therefore reasonable to consider evaluation of monozygotic twin siblings for slit-lamp examination in cases of idiopathic uveitis.

Consent

The patients and their family have verbally consented and assented to publication of the case. Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors have no financial disclosures or conflicts of interest.

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