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Vitritis in Pediatric Genetic Retinal Disorders

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Purpose: To determine which types of pediatric retinal degeneration are associated with inflammatory cells in the anterior vitreous.

Design: Retrospective, observational study in humans.

Methods: Retrospective chart review was performed for pediatric patients with suspected retinal degeneration presenting to a single examiner from 2008 to 2013. Age, visual acuity (VA), slit-lamp examination of anterior vitreous (SLAV), and clinical and molecular genetic diagnoses were documented. Anterior vitreous cells were graded clinically with SLAV from rare cells (1−4) to 1+ (5−9), 2+ (10−30), or 3+ (>30). Cells were also counted in magnified slit beam photographs masked to molecular diagnosis when obtainable.

Main Outcome Measures: Cell counts in SLAV, best-corrected VA, and molecular and clinical diagnoses.

Results: We evaluated 105 charts, 68 of which (64.8%) included SLAV data. Numerous (1+ or greater) cells were present in 22 of 68 patients (32.4%), whereas 4 of 68 (5.9%) had rare cells and 42 of 68 (61.8%) had no cells. The average age between patients with cells, no cells, and rare cells did not differ significantly ($P = 0.25$). The VA averaged 20/124 in patients with cells, 20/143 in patients with no cells, and 20/68 in patients with rare cells ($P = 0.70$). The most frequent diagnoses with cells included Bardet Biedl syndrome (BBS), Leber congenital amaurosis (LCA), and retinitis pigmentosa. The most frequent diagnoses without cells included congenital stationary night blindness (CSNB), LCA, Stargardt disease, and blue cone monochromacy.

Discussion: A nonrandom subset of pediatric retinal degenerations exhibit vitritis. Cells were present in 5 of 5 BBS patients (a progressive degeneration), whereas cells were not detected in any of the 12 patients with CSNB (a stable dysfunction).

Conclusions: Studying vitritis in pediatric retinal degenerations may reveal whether inflammation accompanies progressive vision loss in certain subtypes. Potentially, inflammation could be treated. In addition, SLAV may aid in clinical diagnosis. *Ophthalmology 2015;122:192-199 © 2015 by the American Academy of Ophthalmology.*

Albrecht von Graefe described the ophthalmoscopic appearance and clinical features of retinitis pigmentosa (RP) in detail in 1856, and postulated that heredity played a role. However, it was Donders who, 1 year later, coined the term RP, suggesting an infectious or inflammatory etiology, and thus started a discussion about the etiology of this condition, which continues today.[1] Burstenbinder detected lymphocytes in the retina of pathologic specimens from RP patients early in the 20th century, and his contemporaries described "particles" in the vitreous of living patients, leading some ophthalmologists to espouse an inflammatory etiology even as others pronounced "retinitis pigmentosa" a misnomer.[1] The Ocular Immunology and Uveitis Foundations defines vitritis (vitreitis) as "the accumulation of inflammatory cells or exudates in the vitreous humor" (available: www.uveitis.org/patients/education/glossary/t-z#VITRITIS). Although one cannot say with certainty whether the particulate matter seen on slit-lamp examination of the vitreous represents cells or debris from cell death, the appearance is similar to that in true inflammatory conditions, such as uveitis. This reaction has been reported to decrease in response to local and systemic immunosuppression in the retinal degeneration seen in Juvenile Neuronal Ceroid Lipofuscinosis.[2] The finding that a secondary inflammatory response can exacerbate tissue injury that has a noninflammatory initial cause is well known in other diseases of the nervous system, including stroke, Alzheimer's disease, Parkinson's disease, juvenile neuronal ceroid lipofuscinosis, and ischemia−reperfusion injury.[3−8] It is thus similarly possible that the vitritis seen in retinal degenerations may play a role in the progression of the disease.

Although the presence of antiretinal autoantibodies has been described in some cases of RP,[9−11] and lymphocytes have been detected in vitreous samples from eyes of adults with this disease,[12] there are few investigations into the quantity and timing of vitreous cells, especially as it relates to disease and genotype. Yoshida et al[13] recently reported that 37% of adult patients with RP have an observable anterior vitreous cellular reaction and that stronger inflammatory reactions were more frequently associated with younger RP patients. In the current report, we studied the incidence of anterior vitritis in pediatric retinal degeneration patients with RP as well as other forms of inherited retinal disorders and correlated the presence or absence and intensity of the vitritis with molecular genetic diagnosis. These results suggest that vitreous cells occur in specific genotypes of inherited retinal diseases. Vitritis may have

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diagnostic, prognostic, and therapeutic significance in pediatric retinal degenerations and dystrophies.

Methods

Chart Review

Institutional review board approval was obtained before chart identification. Patients from the pediatric genetic eye disease clinic at the University of Iowa Hospitals and Clinics presenting with suspected retinal degeneration to one of the authors (A.V.D.) from 2008 to 2013 were identified. Suspected retinal degeneration was based on patients' referral diagnoses and features such as nystagmus, night blindness, peripheral vision restriction, abnormal electroretinogram testing, and/or characteristic ophthalmoscopic or physical findings. Data collected included age, Snellen best-corrected visual acuity (VA), and slit-lamp examination of anterior vitreous (SLAV) at most recent visit, and documentation of clinical and molecular genetic diagnosis. Slit-lamp photographs of anterior vitreous (SLAV photos) were analyzed when available. Grading of vitritis at the slit lamp by a single examiner was documented in a similar fashion as prior studies[12,13] where 0 represented no visible cell; rare, 1 to 4 cells per field; 1+, 5 to 9 cells per field; 2+, 10 to 30 cells per field; and 3+, >30 cells per field, as is our routine with all genetic eye disease patients in the pediatric genetic eye disease clinic. Patients with rare cells were examined as a separate category from patients with or without vitritis. Data were analyzed using analysis of variance and the Fisher exact test.

SLAV Photographs

We obtained SLAV photographs for patients with visible cells who could cooperate with anterior vitreous slit-lamp photography. Because it is often possible to rapidly obtain a photograph of vitreous cells when a child is not able to cooperate fully with a more prolonged slit-lamp evaluation including counting cells, we routinely obtain vitreous photographs when slit-lamp examination suggests a cellular infiltrate. Taking standard vitreous photographs at consecutive visits also allows us to compare the vitreous reaction over time. Photographs were obtained by a single ophthalmic photographer using a standardized technique. The SLAV photographs were taken on a Haag-Streit BX 900 photo slit lamp with a Canon 50D DSLR camera back for digital capture. Posterior cell flare images were taken with a slit beam length of 5 mm and a width of 2 mm. All images were captured using the 10× setting at the slit-lamp camera. The slit-lamp beam was projected into the space just behind the crystalline lens at a 30° to 45° angle. The final images were at 16× magnification. In patients with anterior vitreous photographs, cells in the anterior vitreous were counted by an observer masked to diagnosis and genotype using Image J (available: www.imagej.nih.gov/ij/) to mark and count the cells in the magnified slit beam photographs.

Results

Chart Review

We identified 107 charts from children referred to the pediatric genetic eye disease service for a suspected genetic retinal disorder. Two were excluded as asymptomatic, unaffected siblings of patients with retinal degeneration. Clinical data were recorded from the most recent clinical visit, and the age at that visit was documented. Data from SLAV were available from 68 of the 105 patients (64.4%). Slit-lamp examination could not be accomplished in 37 of the 105 (35.6%) owing to young age (the average age of patients with SLAV was 9.3 years; the average age of patients without SLAV was 3.3 years; $P < 10^{-6}$). Of the 68 patients, 42 (62.7%) had no vitritis; 4 of the 68 patients (6.0%) had rare cells, and 22 of the 68 (31.3%) had 1+ or greater cells. The average age of patients with cells, no cells, and rare cells (9.5, 9.5, and 6 years, respectively) did not differ significantly (analysis of variance; $P = 0.255$; Fig 1). Snellen VA averaged 20/124 in the vitritis group, 20/143 in the nonvitritis group, and 20/68 in the rare cells group. Logarithm-transformed best-corrected VA means were 4.338, 4.222, and 3.881, respectively, which were not significantly different when analyzed by analysis of variance ($P = 0.70$; Fig 2). Diagnoses of patients with cells included Bardet Biedl syndrome (BBS; 5/5), Leber congenital amaurosis (LCA; 7/15), RP (5/7), Usher syndrome (2/2), Batten disease (CLN3; 1/1), juvenile X-linked retinoschisis (JXLR; 1/3), and Stargardt disease (1/6).

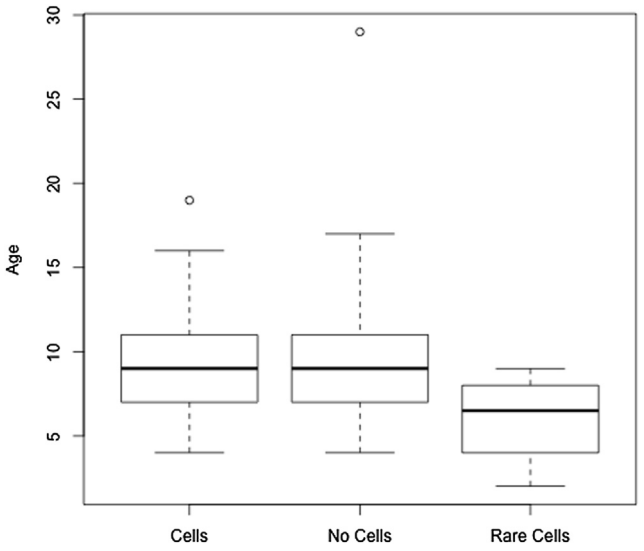

Figure 1. Boxplots of the distribution of age in years in the presence or absence of vitreous cells. Analysis of variance; $P = 0.25$; 2 degrees of freedom. Age on the *y*-axis is given in years.

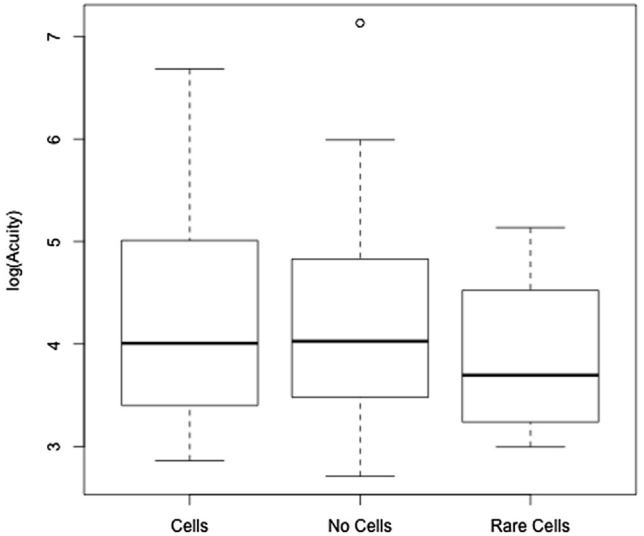

Figure 2. Boxplot of logarithm-transformed best corrected visual acuity in the presence or absence of vitreous cells. Analysis of variance; $P = 0.70$; 2 degrees of freedom.