Establishing the Normative Data Set Necessary for Imaging-Based Childhood Uveitis Surveillance: A Cross-Sectional Study

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Purpose. Anterior segment optical coherence tomography (AS-OCT) is an emerging diagnostic and monitoring tool for anterior uveitis. We investigated AS-OCT findings in the eyes of a large, diverse population of children free of uveitis to establish its potential to "rule out" accurately those without disease.

Methods. In this cross-sectional observational study, image acquisition was performed with swept source AS-OCT (Heidelberg Anterion), using a protocol of 13 B-scans per volume, from 217 children (434 eyes) aged 5 to 15 years, with analysis of acquired images (identification of apparent inflammatory cells, or "cell events") by multiple graders. Outcomes of interest were median and maximum cell event count (MEDCC, MAXCC) per B-scan from each eye and the total cell event count (TCC) per volume scan.

Results. At least one cell event was detected in volume scans of 76% of eyes (329/434) and 87% of children (189/217). The maximum number (MAXCC) per scan ranged from 0 to 6 (median, 2). There was a strong positive association between increasing age (years) and the number of cell events detected within a volume scan following adjustment for gender and iris color (adjusted regression coefficient for TCC 0.5; $P < 0.0001$; 95% confidence interval, 0.4–0.7).

Conclusions. Our findings demonstrate that apparent inflammatory cells are detectable on AS-OCT in the apparently healthy eyes of children and furthermore suggest early life developmental changes in blood–iris barrier stability that merit further exploration. We provide the foundation for the normative data set necessary for establishing the clinical utility of AS-OCT for surveillance of children with inflammatory eye diseases.

Keywords: child, OCT, anterior chamber

Anterior segment optical coherence tomography (AS-OCT) is emerging as a useful diagnostic and monitoring imaging modality for adults and children with anterior uveitis.[1–3] Early investigators used in vitro and animal studies to support their postulate that AS-OCT could detect inflammatory blood cells within the anterior chamber.[4] These "cells" appeared as hyperreflective bodies on cross-sectional AS-OCT images.[5] This was further supported by subsequent replicated reports of the strong correlation of the quantification of these bodies with grading on routine slit lamp–based clinical examination.[5] AS-OCT–based quantification of anterior chamber inflammation, using spectral domain and swept source instruments, has been shown to be repeatable and responsive, holding the potential of providing an objective, sensitive, and community-based assessment tool.[3] Such a tool is particularly needed for the pediatric population, in whom anterior uveitis confers considerable risk of visual and quality of life–related morbidity.[6–8] However, AS-OCT has been shown to detect apparent cells in the eyes of adult and pediatric uveitis patients with clinically inactive disease.[1–4] This "false-positive" rate of AS-OCT detection of inflammation—that is, the detection on AS-OCT of cells, or "cell events" in uveitic eyes that are quiet on slit-lamp examination—has been reported to be high, with a negative impact on positive predictive values.[1,3] The clinical utility of AS-OCT quantification of childhood-onset disease

will be dependent on an understanding of clinical interpretation of the "false-positive" scan. One approach to deepening this understanding is describing the presence or absence of these cell events on AS-OCT images of the eyes of healthy children. We aimed to determine OCT findings for the anterior chamber of an ethnically diverse population of children without eye disease.

Methods

We undertook a prospective cross-sectional study.

Participant Identification and Recruitment

Schools within a primarily urban area in the United Kingdom were included as recruitment sites, with this area purposively sampled to achieve diversity with respect to ethnicity and family socioeconomic status. Two schools (one primary school for children aged 5 to 11 years and a secondary school for those aged 11 to 18 years) were identified as willing participating sites through an approach to a local governmental educational organization ("Enfield School Partnerships"). Eligible children were those aged under 18 years who were enrolled in the school. Ineligible children were those with a known history of inflammatory eye disease as flagged by the child's family. Parents and guardians were asked to give informed consent for image acquisition.

Scan Acquisition

Images of both eyes of each participant were acquired without pupil dilation using the swept source AS-OCT, Anterion model (Heidelberg Engineering, Heidelberg, Germany), using a raster centered at the pupil center with Heidelberg Imaging application. The Anterion is a high-resolution anterior segment SS-OCT device with a 1300-nm light source and scanning speed of 50,000 A-scans/second and axial depth of 14 mm. Piloting using the eyes of children with active inflammation as participants (these patients was not subsequently participants in the study) was undertaken to select scan settings of a 12-mm scan length, 13 B-scans with 768 A-scans per B-scan. The Anterion has automated real-time tracking settings that allow averaging of multiple B-scans taken in the same area to increase the signal-to-noise ratio. Four automated real-time (ART) settings, 1, 4, 8, and 20 (swept source technology allows for lower ARTs versus spectral domain platforms), were piloted using the eyes of patients with differing degrees of anterior chamber cells. An

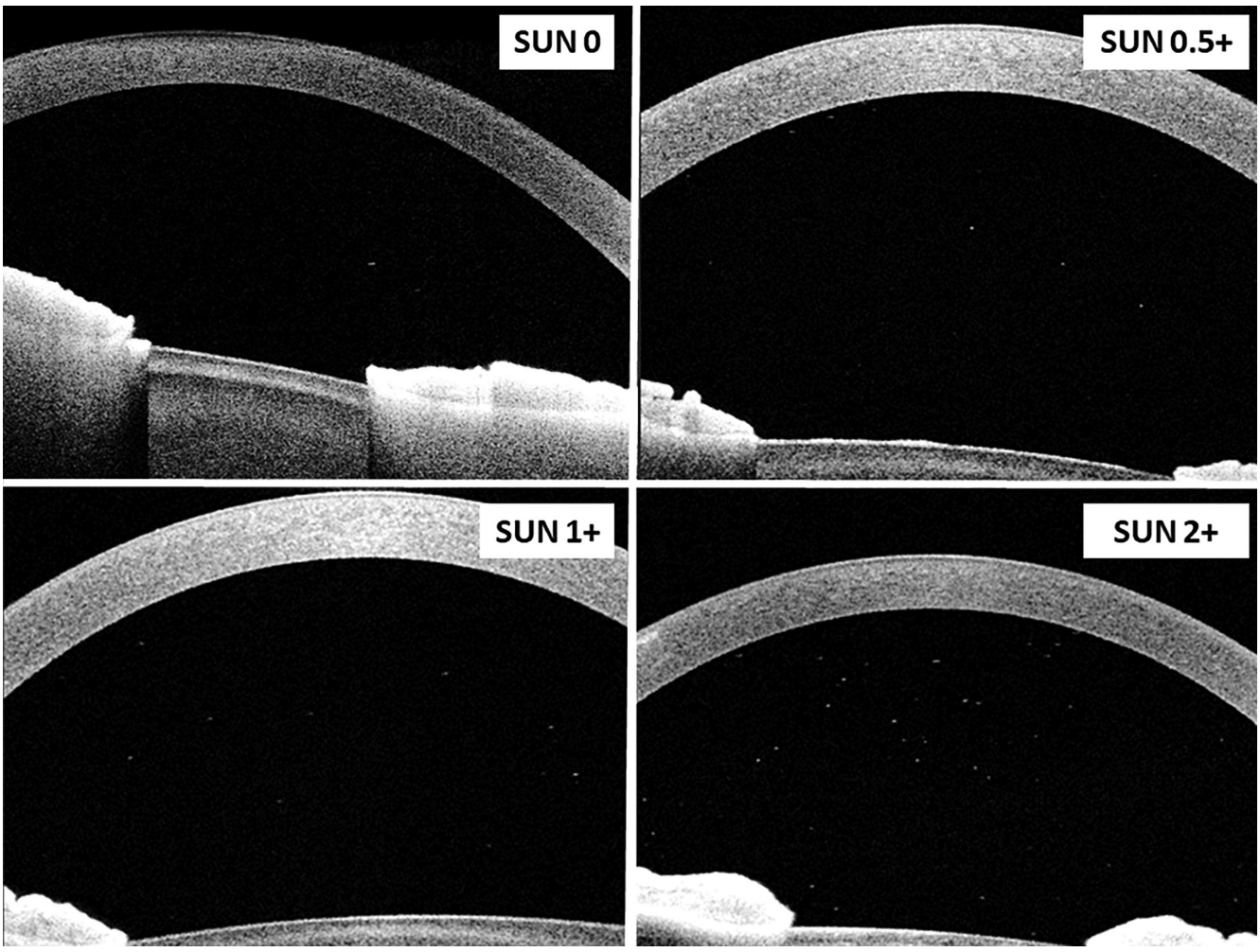

Figure 1. Anterion swept source cross-sectional OCT images of eyes with different levels of anterior chamber inflammation. From 0 on the standardization of uveitis nomenclature (SUN) scale to 2+ on the SUN scale for anterior chamber cell activity. All images acquired from children (aged 8 to 12 years) with anterior uveitis.

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ART setting of 4 and above resulted in capture of visible (to the human eye) hyperreflexive particles against the background signal of the anterior chamber (Fig. 1). An ART of 4 was selected for the scan protocol. Study images were acquired between June 5, 2022, and July 30, 2022.

Image Analysis

Following a process of image quality assessment,[3] each image underwent manual analysis by at least two independent readers to detect and quantify the number of cell events (hyperreflective bodies of ≥2 pixels in size) within the anterior chamber.[1,4,9,10] Readers viewed unaltered cross-sectional scans. Where there was discrepancy between the cell event count made by readers, images underwent semiautomated examination by the senior investigator using ImageJ (National Institutes of Health, Bethesda, MD, USA; thresholding using the IsoData default algorithm where threshold = (average background + average objects)/2),[11] manual drawing of a region of interest, and automated detection of particles ≥2 pixels in size within the region of interest with review of the resultant mask).[1,3,5] At the level of each B-scan, data were collected on the position of the scan in the volume and the number of cell events present. At the level of the eye, data were collected on total number of cell events detectable in the volume. At the level of the child, data were collected on ethnicity (white or nonwhite), sex (male, female, or other), and iris color (graded using a five-level grading scheme, from blue to dark brown).[12,13]

Statistical Analysis

Analysis comprised descriptive analyses of the median and maximum cell event count (MEDCC, MAXCC) per B-scan per eye and the total cell event count (TCC) per volume scan. Cell density scores, calculated using cell counts per image anterior chamber area, also underwent descriptive analysis. Multivariable linear regression analysis, with multilevel adjustment for the within-child correlation of eye-level data, was undertaken to describe associations between cell event counts and the possible explanatory factors of age, gender, ethnicity, and iris color. Correlations between factors were investigated using nonparametric tests (χ^2, Mann–Whitney *U*, and Spearman), with a *P* value threshold of 0.05 selected as indicative of a statistically significant correlation. Multivariable models were constructed using conventional forward and backward stepwise regression and included variables significant at a 10% level in initial univariable analysis. Where there was correlation between independent variables ($P < 0.05$), relationships were explored using interaction terms. Where only one variable was found to reach statistical significance ($P < 0.10$) on univariable modelling, adjustment was made for the other putative biological correlated factors. Factors were retained in the multivariable model if they altered the risk ratio estimate by more than 10% or were independently associated at a 5% significance level and if there was no significant correlation between dependent variables. Analyses were undertaken using Stata (version 15.1; StataCorp, College Station, TX, USA).

The research followed the tenets of the Declaration of Helsinki. Institutional review board/ethics committee approval was obtained. Study approvals were granted by the NHS Health Research Authority (19/SC/0283). Participants were included only after individual informed parental consent.

Results

Images were acquired from a total of 217 children aged between 5 and 15 years (median, 11.3 years). Half of the children (108, 50%) were female, and 8% of students were black (18/217), 10% (22) were Southeast Asian, and 75% (162) were from a white ethnicity background, with the remaining 7% (15) from other backgrounds. Iris colors were blue, blue-green, hazel, brown, and dark brown in 21% (46), 6% (13), 21% (46), 40% (87), and 12% (25) children, respectively. There were no associations between the ages or gender of children and iris color or ethnicity, but there was a correlation between ethnicity and iris color. A total of 434 volume (13-line raster) scans were acquired (i.e., a total of 5642 analyzed individual B-scans). Of the reviewed cross-sectional scans, disagreements on cell events occurred across 102 scans (1.8%), which then underwent semiautomated analysis.

Presence of Cells on AS-OCT

At least one cell event was detected in volume scans of 76% of eyes (329/434) in 87% of children (189/217) (Fig. 2). The median number of cell events per scan per volume (MEDCC) ranged from 0 to 2 (median, 0), while the maximum number (MAXCC) per scan ranged from 0 to 6 (median, 2). TCC per eye ranged from 0 to 28, with a median of 4. The median cell event density per scan per volume ranged from 0 to 5.1×10^{-6} cells per pixel (median 0), while the maximum per scan ranged from 0 to 18.3×10^{-6} (median, 3.2).

Distribution of Cells Within the Anterior Chamber

Within the volume scans, there was a tendency for cell events to be identified within the more centrally positioned B-scans (Fig. 3), although this was less pronounced when adjustment was made for the larger anterior chamber area present in the more centrally positioned scans.

Associations Between Cell Event Counts and Child-Level Characteristics

Although gender, ethnicity, and iris color were not associated with MEDCC, MAXCC, or TCC on univariable regression analysis (Table), there was a statistically significant positive association between increasing age in years and the number

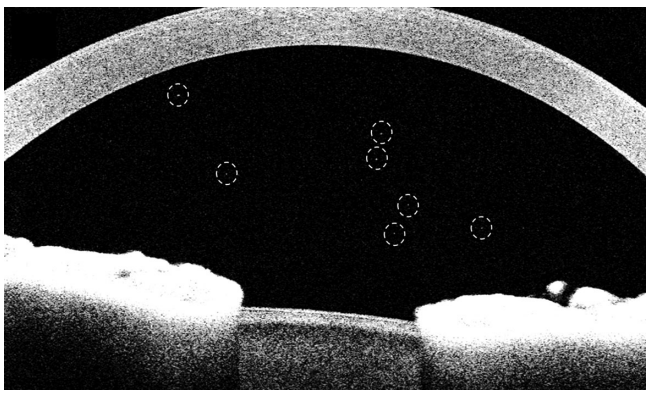

Figure 2. Cross-sectional/B-scan swept source AS-OCT of eye of a healthy 13-year-old. Captured cell events highlighted by *white circles*.

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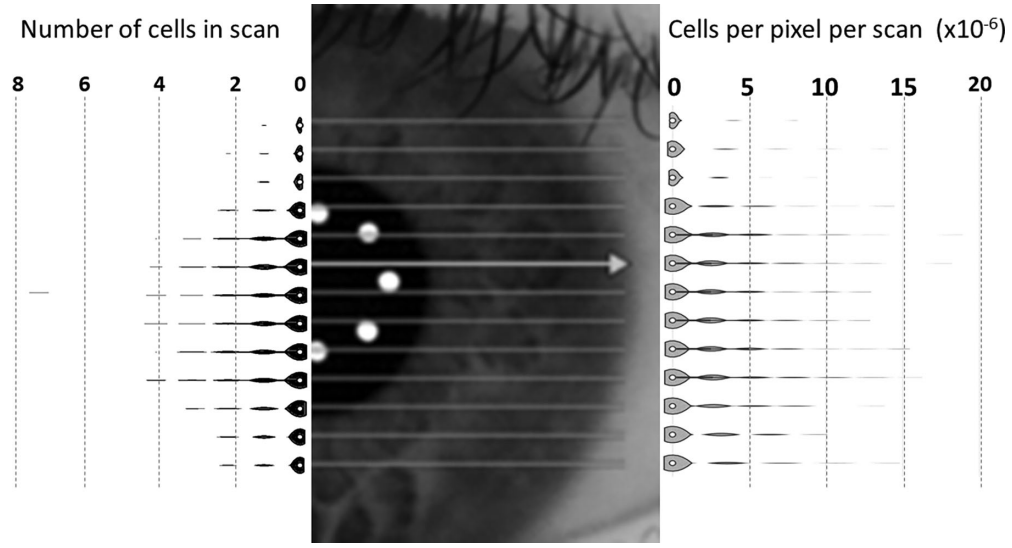

Figure 3. Violin plot showing cell event count and cell event density within acquired cross-sectional OCTs at different horizontal positions across the eyes. The *white dot* indicates median number of cells at each horizontal position across all eyes.

Table. Correlation Between Child-Level Factors and Total Cell Event Count on Volume Scan (TCC)

Factor	Correlation Coefficient*	95% CI	*P* Value
Female sex	0.6	−0.5 to 1.6	0.3
Nonwhite ethnic origin	1.8	−0.8 to 3.9	0.5
Iris color			
Blue	—	—	—
Blue-green	0.5	−1.8 to 2.9	0.6
Hazel	0.8	−0.9 to 2.5	0.3
Brown	−0.1	−1.4 to 1.3	0.9
Dark brown	0.2	−1.6 to 2.1	0.8
Age (increasing, in years)	0.5	0.3 to 0.6	<0.0001

*Multilevel regression models to account for clustering of data within child.

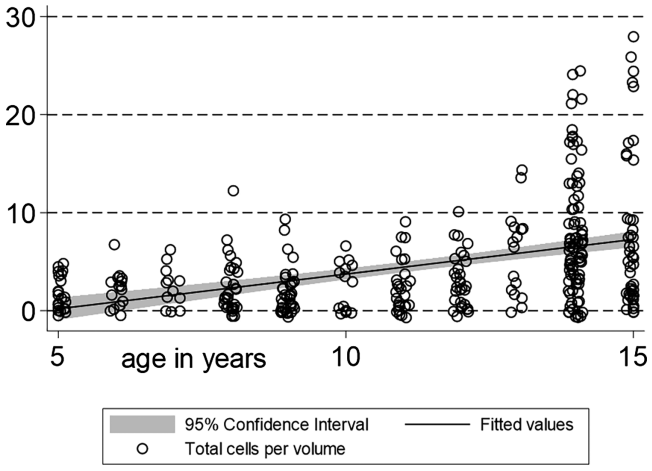

Figure 4. Correlation between age at scan acquisition and TCC.

of cells detected within a volume scan (Fig. 4). This association reached statistical significance (regression coefficient with multilevel adjustment for TCC 0.5 cells for each increasing year of age; $P < 0.0001$; 95% confidence interval [CI], 0.3–0.6 and for MEDCC 0.02 cells for each increasing year of age; $P < 0.0001$; 95% CI, 0.01–0.03). This association was robust following adjustment for gender and iris color (adjusted regression coefficient for TCC 0.5; $P < 0.0001$; 95% CI, 0.4–0.7 and for MEDCC 0.02 cells; $P < 0.0001$; 95% CI, 0.01–0.03). There was also positive correlation between increasing age in years and maximum cell density per scan per volume (correlation coefficient 0.47 × 10^{-6} cells per pixel; 95% CI, 0.37–0.59; $P < 0.001$) and maximum cell density per scan (correlation coefficient 0.09; 95% CI, 0.06–0.12; $P < 0.001$). There was no correlation between cell density and gender, ethnicity, or iris color.

Discussion

From this prospective cross-sectional study, we report that most (87%) of the apparently healthy eyes of children have findings on SS-AS-OCT volume scans that could be considered to represent inflammatory cells. We report the absence of an association between the presence of cells and gender, ethnicity, or iris color. Cell events were more likely to be seen in older children, with an estimated additional cell seen on a cross-sectional image for each additional 5 years in age, and additional cell seen across a volume scan with each additional 2 years in age.

This relatively large study describes OCT findings among an ethnically diverse cohort of school-age children but is limited by the unimodal approach undertaken with regards to assessment of anterior chamber inflammation. Slit-lamp examination (SLE) was not undertaken for recruited children. This pragmatic decision, made to facilitate study delivery, has resulted in an inability to report on the normative SLE findings in otherwise healthy childhood anterior chambers or a comparison of AS-OCT and SLE findings. It is possible that some of the school children who underwent imaging had undiagnosed asymptomatic anterior uveitis, for example, due to an associated systemic disorder such as juvenile idiopathic arthritis, as children with a personal or family medical history of inflammatory systemic disorders were not excluded from this study, Undiagnosed anterior uveitis may explain the potential presence of inflamma-

tory cells on AS-OCT. However, with an estimated annual UK incidence of 5/100,000,[14] undiagnosed disease cannot account for the finding of detectable inflammatory cells in most of our participants. Additionally, even if there had been "outlier" cell event counts due to true cases of disease present in this apparently healthy population, these outliers would not have had an effect on the median OCT-based cell event count, which does support age-related change. It has been suggested that refractive error can result in a higher risk of pigment in the anterior chamber, although this has not been reported outside adults with pigmentary dispersion syndrome.[15] As refraction status and axial length were not measures in this study, our findings are not able to address this postulated association.

It is possible that if a precise, objective metric of iris color had been used in our study, a correlation between iris pigmentation and AS-OCT cell presence might have been detected, if this association exists. Such a metric has yet to be validated for children. We reported the absence of a statistically significant difference between irides at the "extreme" ends of the validated subjective scale used in this study (i.e., blue versus dark brown irides). The median (SD) of TCC was 3 (5.2) and 4 (5.6), respectively, for blue and dark brown irides, with sample sizes sufficient for detection of a difference in median TCC of 2 cells, with power = 0.90, $\alpha = 0.05$. This supports the absence of a type II error (i.e., that there is indeed no "true" association between iris color and cell event count on 13-line AS-OCT volume imaging of the healthy eyes of children).

There was also no use of laser flare photometry (LFP) within our study. LFP is a long-established objective metric with high repeatability and predictive power for poor outcomes in childhood uveitis.[16] Use of LFP would have provided a metric for blood–iris barrier status. Measurements of aqueous signal intensity derived from AS-OCT (aqueous-to-air relative intensity [ARI] index) have also been found to found to correspond with LFP,[9] although with decreasing correlation strength between ARI index and LFP at lower levels of LFP, suggesting lower accuracy of ARI index at low levels of inflammation. The use of LFP has not been widely adopted within clinical settings.[17] The need for an entirely dark room and for patient immobility to allow the taking of multiple measurements can be an obstacle within clinical settings, let alone in a school-based study. Additionally, a future wider adoption of AS-OCT for clinical care will involve its use as a surveillance tool outside of secondary and tertiary care, in settings where there will be no specialist available to undertake slit-lamp or LFP examination. Conversely, OCT has already been widely adopted within community-based eye care health centers.[18]

While our study has a smaller sample size than many biometric normative studies, such as those that underpin pediatric child growth chart development,[19] the key findings of the presence of AS-OCT cells and increasing number with age in healthy children remain robust even if the ability to define precisely the maximum number of cells at different stages of childhood and adolescence is limited.

Childhood-onset disease accounts for only 1% of cases seen in adult uveitis clinics.[20,21] However, it accounts for 10% of cases of uveitis-related sight impairment among adults.[22,23] The strongest predictor of poor visual outcomes in childhood-onset uveitis is the presence of established ocular structural complications at diagnosis.[14] These complications are due to delayed diagnosis in asymptomatic children or in children too young to be able to reliably report symptoms.[14] Surveillance programs have been established for children known to be at risk of uveitis in an attempt to avoid uveitis-related sight loss in children.[24–26] The largest group of children at risk are the approximately 1 in 1000 children diagnosed with juvenile idiopathic arthritis, or JIA, every year.[27] With the preexisting global staffing crisis in ophthalmology exacerbated by the COVID-19 pandemic, delivery of this surveillance program is increasingly challenging.[28]

AS-OCT is emerging as a tool potentially able to provide an imaging-based, community-based resource for JIA uveitis surveillance (analogous to the imaging-based, community-based programs for national diabetic eye screening undertaken in settings such as Finland, Singapore, and the United Kingdom, albeit on a much smaller scale). The utility of AS-OCT in ruling in or ruling out the presence of clinically significant inflammation will be dependent on building an understanding of the findings in populations without disease. There is a growing body of evidence on findings in children with known anterior segment inflammation, with evidence of repeatable, responsive AS-OCT–based quantification of anterior chamber inflammation across all levels of disease severity (Fig. 1). Our findings provide a foundation for this understanding as we build toward implementation of this novel application. Different AS-OCT platforms (e.g., swept source versus spectral domain instruments, or those systems with different scanning speeds and different axial resolution limits) and different imaging protocols (e.g., a central single-line scan versus a multiple-line volume scan) are likely to result in differences in the quantification of cell events on AS-OCT.[29] It is possible that a single-line acquisition protocol would have resulted in a lower total cell event count for healthy eyes, but as cells were more commonly seen in central scans, our overall conclusions are likely to have been similar with that approach. Nevertheless, future investigators must explicitly describe imaging platforms and acquisition protocols as we grow the evidence base for this modality beyond the foundation work provided in this study and by other groups.[2–5,9,29]

AS-OCT will also be of use in disease monitoring in childhood uveitis, particularly with regards to defining disease control and disease remission. The threshold for inactive childhood uveitis ("controlled" disease) differs among international groups.[30] The American College of Rheumatology defines controlled childhood anterior uveitis as anterior chamber inflammation at the level of standardization of uveitis nomenclature (SUN) grade <1+ anterior chamber cells (i.e., inclusive of grade +0.5, 1–5 cells seen in a 1-mm slit-lamp beam).[25,31] Conversely, the Single Hub and Access Point for Pediatric Rheumatology in Europe and the Multinational Interdisciplinary Working Group for Uveitis in Childhood define inactive disease as "0 (zero) inflammatory cells in the anterior chamber" on slit-lamp examination.[26,32] Our findings in this study of children without eye disease suggest that an anterior chamber that is consistently free of inflammatory cells on anterior segment OCT will be hard to achieve, particularly for older children, with a resultant risk of overtreatment. This is supported to some extent by the finding of inflammatory cells in the eyes of children with clinically inactive disease in the context of a diagnosis of childhood anterior uveitis.[2,3,29] However, as slit lamp–based grading of anterior chamber inflammation is known to be open to considerable intra- and intraobserver variability, in some of these cases, there may have been misclassification of disease status. Further work will build our understanding

of anterior segment OCT findings in clinically inactive eyes. As adult anterior uveitis is one of the most common presentations to eye casualty departments, AS-OCT will also have an impact beyond pediatric disease.

In summary, our findings of apparent immune cells in the eyes of healthy children have consequences for the wider use of AS-OCT–based screening for children at risk of uveitis and for setting therapeutic targets for disease control in childhood uveitis. Future multicenter, multiplatform validation of our work will support the improved precision necessary for clinical utility. The association of age with cell count suggests an early life aging-related change in blood–iris barrier stability, which is worthy of further exploration.

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