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Automated Analysis of Anterior Chamber Inflammation by Spectral-Domain Optical Coherence Tomography

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Purpose: This study was designed to determine the feasibility of anterior segment optical coherence tomography (AS-OCT) to objectively image and quantify the degree of AC inflammation.

Design: Prospective evaluation of a diagnostic test.

Participants: Patients with anterior segment involving uveitis.

Methods: Observational case series of patients with uveitis. Single-line and 3-dimensional (3D) volume AS-OCT scans were manually graded to evaluate for the presence or absence of cells in the AC. Clinical grading scores were correlated to the number of cells seen in each line scan. An automated algorithm was developed to measure the number of cells seen in the 3D volume scan and compared with manual measurements and clinical grading scores.

Main Outcome Measures: Degree of anterior segment inflammation.

Results: A total of 114 eyes from 76 patients were imaged, 83 eyes with line scans and 31 eyes with volume scans. The average number of cells on line scans was 0.13 for grade 0, 1.2 for grade 1/2+, 2.6 for grade 1+, 5.7 for grade 2+, 15.5 for grade 3+, and 41.2 for grade 4+. Spearman correlation coefficient comparing clinical grade with the individual AS-OCT line scans was 0.967 ($P < 0.0001$). The range of cells in the automated cell count of 3D volume scans was 13.60 to 1222; the range for manual cell counts was from 9.2 to 2245. The Spearman correlation coefficients were $r = 0.7765$ ($P < 0.0001$) and $r = 0.7484$ ($P < 0.0001$) comparing the manual and automated cell counts with the clinical grade, respectively. Spearman correlation coefficient comparing the automatic cell counts with manual cell count in the 3D volume scan was 0.997 ($P < 0.0001$).

Conclusions: Anterior segment OCT can be used to image and grade the degree of AC inflammation. Clinical grading strongly correlates with the number of cells on AS-OCT line scans and volume scans. The automated algorithm to measure cell count had a high correlation to manual measurement of cells in the 3D volume scans. This modality could be used to objectively grade response to treatment. *Ophthalmology 2015;■:1−7 © 2015 by the American Academy of Ophthalmology.*

Supplemental video is available at www.aaojournal.org.

Slit-lamp examination is currently the standard of care for recording the degree of anterior chamber (AC) inflammation in cases of uveitis.[1] The number of visible cells in the AC are counted and graded on a scale of 0 to 4 based on the Standardization of Uveitis Nomenclature (SUN) Working Group.[2] This allows for a standardized method for comparing the degree of inflammation in clinical trials. However, this method relies on the subjective evaluation of the number of cells by a trained observer and thus is susceptible to interobserver variation.[3] Although the interobserver agreement within 1 clinical grade is high (kappa range, 0.81−1.00), the agreement within the same grade is low (range, 0.34−0.43).[3] The variability is further compounded by differences in equipment at different clinical sites, which has been shown to affect the ability to accurately visualize cells in the AC.[4]

The wide range of cells per high-power field in grade 3+ (26−50 cells/high power field) and grade 4+ (>50 cells/high power field) limits the ability to accurately determine a small change within these higher grades of inflammation. As such, significant clinical improvement could occur within the higher grades of inflammation once treatment is initiated, but not detected using the SUN criteria. On the basis of the SUN criteria, "improved activity" is a 2-step improvement or resolution to grade 0.[2] Thus, an improvement from 2+ cells to 0.5+ cells is considered the same improvement as 3+ cells to 1+ cells. In these examples, the amount of improvement in pure cellular counts is different: 16 to 25 cells to 1 to 5 cells versus 26 to 50 cells to 6 to 10 cells, respectively. In addition, within grade 3+, an improvement of 50 to 26 cells would not meet the SUN definition of improved activity, whereas an improvement of 16 to 5 cells (grade 2+ to 0.5+) would be defined as improved. Ultimately, the lack of a linear grading scale could mean that clinically relevant improvements are missed. In clinical trials, this limitation could mean a

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novel drug therapy is termed a failure despite having real clinical improvement.

There have been a few studies evaluating the feasibility of imaging the AC of the eye to assess the degree of inflammatory reaction using optical coherence tomography (OCT).[5–8] All of the studies reported in the literature used a time domain OCT device with axial and transverse resolutions (~17 μm in tissue) larger than individual white blood cells (as small as 7–9 μm).[9] Newer spectral-domain OCT (SD OCT) devices have both axial and transverse resolutions in tissue that are finer than time domain OCT.[10,11] Spectral-domain OCT technology has been adapted for imaging the AC of the eye and provides a resolution fine enough to distinguish individual white blood cells.[12,13] In addition, the use of high-speed SD OCT devices allows for the construction of 3-dimensional (3D) maps of the AC of the eye. These 3D maps can then be analyzed to compute the total number of cells in the AC.

The purpose of this study was to determine the feasibility of using SD OCT to objectively image and grade the degree of AC inflammation in eyes with inactive and active uveitis. We also sought to develop an automated method to quantify the amount of cells in the AC on 3D SD OCT scans to develop a continuous measure of AC inflammation.

Methods

Subjects

This was an observational, prospective, consecutive case series of patients presenting to the Cleveland Clinic Cole Eye Institute uveitis clinic with active anterior segment (AS) uveitis between June 2012 and June 2013. Patients were excluded if they had any corneal opacity preventing adequate imaging of the AC. Both eyes were included if there was a diagnosis of uveitis involving the AS in both eyes. Written informed consent was obtained before undergoing AS-OCT imaging. This study had prior approval from the Cleveland Clinic Institutional Review Board, complied with the Health Insurance Portability and Accountability Act of 1996, and followed the tenets of the Declaration of Helsinki (clinicaltrials.gov identifier NCT01746537).

Clinical Examination

A detailed slit-lamp examination was performed in all cases by a uveitis specialist (C.Y.L. or S.K.S.). The degree of inflammation in the eye was graded using the SUN grading system with a 1×1-mm slit-lamp beam centered on the center of the cornea. In short, the number of cells seen in a standard field defined by a 1×1-mm slit beam were counted. The ordinal scale was 0 for no detected cells, 0.5+ for 1 to 5 cells per field, 1+ for 6 to 15 cells, 2+ for 16 to 25 cells, 3+ for 26 to 50 cells, and 4+ for >51 cells. Any other ancillary testing was performed as deemed necessary for clinical diagnosis. The presence or absence of pigment or other changes was recorded. The clinical grade was recorded before performing OCT imaging, and the grade was not changed on the basis of the result of OCT imaging.

Optical Coherence Tomography Examination

All patients were imaged on the RTVue-100 (Optuvue, Inc, Fremont, CA) by one investigator (K.B.). The RTVue-100/CAM is an SD-OCT device with a corneal adaptor module used to image the cornea and anterior segment of the eye. It has a scanning speed of 26 000 A-scans/second, with an axial resolution in tissue of 5 μm. The RTVvue-100/CAM device includes 2 cornea lens adapters for imaging the cornea and AC of the eye. The low-magnification corneal lens adaptor was used for this study. This lens provides a scan length from 2 to 6 mm and a scan depth of 1.96 mm in tissue for corneal scanning and AS-OCT.

All line scans were centered on the corneal apex with the posterior corneal boundary visible on all scans. Poor-quality or misaligned scans were retaken without saving. All OCT scans contained the posterior corneal boundary, a highly reflective spike corresponding to the corneal apex, and some scans contained portion of the iris or lens. High-resolution line scans consisted of a 6-mm single B-scan at the central cornea. Three-dimensional volume scans consisted of a 6×6-mm cube consisting of 512 B-scans each with 128 A-scans. All OCT images were evaluated in gray-scale. Volume scans were centered inferior to the corneal apex to avoid the superior lid margin and lashes.

Automated Algorithm

An automated algorithm was developed by ImageIQ (Cleveland, OH) using a library of ImageIQ filters in conjunction with a development platform provided by ImagePro Plus (Media Cybernetics, Rockville, MD) to scan through all of the OCT scans comprising a 6×6-mm volume scan and counting the number of cells seen in the AC. The algorithm first determined the location of the cornea and the hyperreflective stripe representing the central cornea and excluded these regions from the cell count. It then went through each scan and counted the number of hyperreflective spots seen in the scan above a certain threshold reflectance value. The number of hyperreflective spots was then tallied and output as a final cell count. The total volume measured was also calculated by the automated algorithm. The number of cells counted per cubic millimeter were then calculated. Size is an output of the algorithm, but it is not reported in this article because of uncertainty in actual segmented cell size that could be altered by low signal to noise ratio due to partial averaging around boundaries and streaking caused by cell movement.

For segmentation of the cornea, a set of iterative morphologic "closing" (2-dimensional and 3D) filters were applied to each scan slice to generate a more uniform appearance of the cornea. Subsequently, a background extraction algorithm was applied that smoothed the cornea and removed any smaller brighter objects (i.e., cells) followed by a Fourier-based high-pass filter with a large window/kernel size to normalize intensity and enable a fixed threshold extraction of the cornea. Last, any streaks of reflectivity were segmented using a Fourier band-pass filter and eliminated. Segmented objects were defined as cells if they were between 3 and 50 pixels in area. No adjustments to the algorithm were made between cases analyzed. There is an intentional dilation of the corneal boundary to remove precipitates and the disjoint, often bright boundary of the cornea that can be segmented as cells.

Grading and Statistical Analysis

The high-resolution single line scans were evaluated by one of the investigators (S.S.) masked to clinical grade to determine the number of hyperreflective spots seen in the scan. Each of the individual B-scans in the 3D volume scans was examined to count each hyperreflective spot. The manual grading of the number of hyperreflective spots on the high-resolution line scan and in the 3D volume scans were compared with clinical grading by Spearman correlation coefficients. The automated cell count determined by the algorithm for each of the 3D volume scans was compared with the manual cell count by Spearman correlation coefficients.