Imaging based uveitis surveillance in juvenile idiopathic arthritis: feasibility, acceptability and diagnostic performance

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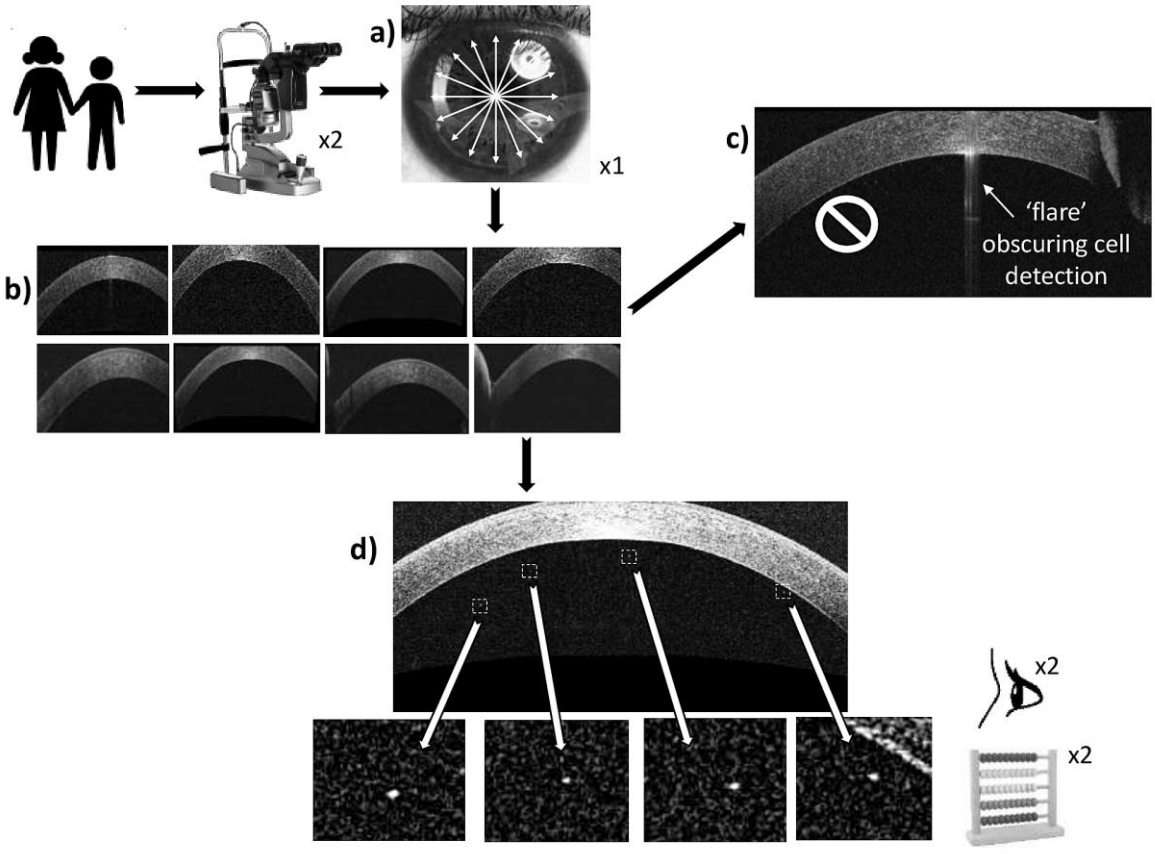

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Abstract

Objective Children with juvenile idiopathic arthritis need regular examinations for uveitis to avoid visual morbidity from the most common extra-articular manifestation of disease. We investigated the feasibility, acceptability and performance of optical coherence tomography (OCT) imaging based diagnosis of uveitis.

Methods Observational cross-sectional study involving children with and without uveitis. Children underwent routine clinical examination and acquisition of anterior segment (AS) OCT scans images of intraocular inflammatory cells. Acceptability of image acquisition was assessed using a visual analogue scale, and duration of image acquisition. Inter and intra-observer variability of manual counting of acquired images (Bland-Altman limits of agreement), correlation between imaging and routine assessment, and sensitivity and specificity of AS-OCT detection of active inflammation were assessed.

Results Of 26 children aged 3yrs to 15yrs (median 8yrs) who underwent imaging, 12 had active inflammation. All patients rated acceptability of image acquisition as at least 8·5/10. Time taken to acquire images ranged from 1·5mins to 22mins (median 8mins). There was good positive correlation between clinical assessment and image based cell quantification (R^2=0·63, p=0·002). Sensitivity of AS-OCT manual image cell count for diagnosis of active inflammation was 92% (95% Confidence interval 62%-99%), specificity 86% (58%-98%), and negative predictive value (‘ruling-out’ uveitis) 92% (65%-99%).

Conclusion Non-contact, high-resolution imaging for JIA uveitis surveillance is feasible, acceptable to patients, and holds the promise of transforming paediatric practice. Further work is needed to determine the analytic and clinical validity of AS-

OCT quantification of active inflammation, and the clinical and cost-effectiveness of imaging based disease monitoring.

Keywords

Child

Juvenile Idiopathic Arthritis

Uveitis

Imaging

Diagnosis

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common inflammatory rheumatological disorder of childhood,(1) and uveitis (intraocular inflammation) is the most common extra-articular manifestation of disease.(1) Uveitis results in impaired vision in up to a fifth of affected children, with visual complications typically being a result of delayed diagnosis.(2) European and American guidelines recommend a formal uveitis surveillance protocol for all patients in whom a JIA diagnosis is being considered, to enable early detection of this often asymptomatic but potentially blinding disease.(3) Disease activity in anterior uveitis (the most common manifestation of JIA related uveitis) is currently assessed within hospital eye services using slit-lamp biomicroscopic examination,(4) a semi-quantitative and subjective assessment. Imaging based assessments, such as joint ultrasonography and MRI, have provided sensitive, repeatable and clinically meaningful disease metrics for inflammatory disease, supplementing clinical examination.(5) Optical coherence tomography (OCT), a non-contact, non-invasive, high speed, high resolution modality with long established use for imaging the posterior segment of the eye. It is now by far the most commonly used ophthalmic imaging procedure.(6) A relatively recent modification has recently been used to image the anterior chamber,(7) with identification of anterior chamber inflammatory cells as hyper-reflective dots. The feasibility of such image acquisition in children is unclear. We aimed to investigate the feasibility, acceptability and diagnostic performance of imaging based disease monitoring for childhood anterior uveitis.

METHODS

This was an observational cross sectional study involving children (aged under 18 years) with and without uveitis. Study approvals were granted by the national Health

Research Authority (18/LO/0252), and local Institutional Research Boards. This research followed the tenets of the Declaration of Helsinki.

Study population

Two groups were recruited. Group one comprised children with a diagnosis of chronic anterior uveitis, who were recruited from a specialist paediatric uveitis care centre in London, England between 2017 and 2018. Group two comprised children without a diagnosis of uveitis, and were siblings of patients attending the outpatient department (within which ophthalmology, audiology and otolaryngology care is provided) for any reason. This latter group enabled an investigation of the normative range of hyper-reflective dots on AS-OCT mages of children's eyes.

Exclusion criteria: Children with a previous history of ocular trauma, any ocular inflammation, or juvenile idiopathic arthritis were excluded from Group two. Children aged under two years (and thus typically unable to undergo slit lamp examination without restraint) were excluded.

Clinical assessment: Routine clinical assessment of the anterior chamber was carried out by two senior ophthalmologists (ALS, CE) using the same slit lamp (Haag Streit BM 900). The ordinal Standardised Uveitis Nomenclature (SUN) anterior chamber activity cell count grade was used to assess inflammation. The SUN cell grade runs from 0 (no cells seen within a central 1mm long beam) to +0·5 (1-5 cells seen), +1 (6-15), +2 (16-25), +3 (26-50), and ends at a highest level of inflammation of +4 (more than 51 cells seen by the clinician within the beam).(4)

Image acquisition

A spectral domain optical coherence tomography (OCT) scanner with an axial resolution of five microns, was used (Optovue AngioVue, Optovue Inc, Freemont California). Cross sectional anterior segment OCT (AS-OCT) scans of the anterior

chambers were acquired (ALS), imaging to a depth of 1·96mm, or two thirds of the average mid-childhood anterior chamber depth.(8) Eight cross-sectional images were acquired in an asterisk formation centred on the corneal apex. Children aged eight years old and over positioned their head at the machine and were asked to fixate the eye being tested (test eye) on the machine generated fixation beam. Younger children were asked to fixate the non-test eye on a cartoon played on a smartphone held in a position so as to align the test eye within the scanning window. Image acquisition time, defined as the duration from first chin placement by the child to successful capture of images of sufficiently high quality to enable image analysis, as judged by one trained clinician (ALS), was measured. Acceptability of the acquisition process for the child and accompanying parent or carer was captured using the question “What did you think of the scan’, which was completed following reiteration of study aims using a standardised study information leaflet. A 10 centimetre scale visual analogue scale (VAS) was used, running from 0 (not acceptable, or crying face) to ten (completely acceptable, or smiling face). The VAS was completed by all children aged over six years, with proxy completion by parents or carers only for younger children.

Image analysis

Images were analysed manually, and were reviewed independently by at least two examiners, with each examiner undertaking two viewings of the stored and anonymised images, separated by at least two weeks. All examiners (comprising one ophthalmologist, one optometrists, and one medical student) were trained using a separate set of AS-OCT images of confirmed anterior chamber inflammation. Eight cross sectional images of three eyes of two children with known anterior chamber

inflammation were selected by the study lead (ALS) as training images. There was no other additional training provided.

For manual image analysis, all visible hyper-reflective dots brighter than the background noise and / or larger than two pixels were counted. There were no restrictions of size, but any dots with irregular margins suggestive of cell clumping were counted as two cells. Hyper-reflective dots immediately anterior to the anterior iris signal were discounted as artefact. Examiners were blind to child identify and the results of clinical assessment. Images were judged ungradable if there were artefacts seen within the viewing envelope formed by the inner surface of the cornea and the superior border of the iris. Total cell count across eight images, and median cell count per image per eye was recorded.

Statistical analysis

Descriptive analysis of all outcome measures was undertaken. Repeatability of manual counting of acquired images was described using the intra-class correlation coefficient two way mixed effect model (intraobserver reliability), Cohen's kappa statistic (interobserver) and the Bland-Altman limits of agreement (intra and interobserver). All analysed imaged were used for analyses of count repeatability. Effectiveness of imaging-based diagnosis of inflammation was assessed using the diagnostic performance of AS-OCT detection of active inflammation versus the reference standard of slit lamp based assessment. One eye was chosen at random for each child for inclusion within the analysis of OCT as a diagnostic tool versus slit lamp examination. Only eyes in which a full set of eight good quality images had been obtained were used for assessment of diagnostic performance. Cases were AS-OCT 'positive' if any inflammatory cells had been noted on any of the eight cross

sectional images, and were slit lamp ‘positive’ if any clinician had graded them as active on biomicroscopic examination of the anterior chamber.

Correlation between imaging acquired cell count and clinical assessment of inflammation was assessed using a multilevel linear regression model with correction for within-child correlation to account for the clustered structure of the eye level data for those children who had undergone assessment in both eyes. Accordingly, where data from both eyes was available, both eyes were included in these analyses. Analyses were undertaken using Stata (version 15, StataCorp, College Station, Texas).The study was supported by a ‘Generation R’ Young Persons Advisory Group and a patient family advisory group. Young people and patients co-designed the study to ensure minimisation of the burden of study participation for patients and their families.

RESULTS

A total of 26 children aged 3yrs to 15yrs (median 8yrs, 18 female, 8 male) underwent imaging of 52 eyes (figure 1). This included 19 children with a known diagnosis of uveitis (bilateral in 16), of whom 12 had JIA associated uveitis. The remaining seven children had idiopathic uveitis. Of the 19 children, 12 had active anterior inflammation as confirmed by two examiners at the slit lamp, with all eyes scoring ≤1+ anterior chamber inflammation on the slit lamp SUN scale.

Feasibility and acceptability

Time taken to acquire images from both eyes ranged from 1·5mins to 22mins per child (median 8min) with a trend towards faster acquisition times as the study progressed (trend R^2=0.4092, p<0.001, supplemental figure S1). The patient with the longest acquisition time, 22 minutes (patient number 3) was aged 3 years old. The other two younger patients (aged 5 and 4 years) had successful acquisition of images from both eyes within 8mins. Of the 52 imaged eyes, a full quota of eight analysable images was acquired in 44 (figure 1), with a total of 377 images undergoing manual cell counting. Patient acceptability scores for the acquisition process were acquired from all those imaged, with 23 older children self-rating, and the remaining 3 children having proxy rating completed by parents. Acceptability scores ranged from 8·5 – 10 /10, median 9·5.

Repeatability of manual counting

Across 'positive' single images median count per image was 2 (range 1 – 9). There was good intraobserver image agreement, ICC=0·81, 95% CI 0·63 – 0·98), Bland Altman limit of agreement (LoA) indicating agreement of 1 cell across different counts repeated by the same observer (LoA= -1·1 cells (95% CI -1·4 to -0·8) to 1·0 (0·7 to 1·4)). There was moderate agreement on cell count between observers, κ= 0·46 (95% CI 0·28 – 0·63, p<0·001), with evidence of a wider limit of agreement, LoA= -2·5 cells (95% CI -3·1 to - 1·9) to 1·5 (0·8/2·1). There was disagreement between image observers on the presence of intraocular cells in 25 of the 377 reviewed images (6.6%).

Diagnostic performance indices of AS-OCT detection of inflammation

The 44 eyes with a full quota of eight analysable images were used in the analysis of diagnostic performance. There was disagreement between image observers on

whether cells were detected on OCT imaging in 6/44 eyes (supplemental table). There was disagreement between clinicians on whether an eye was active or inactive on SUN slitlamp grading in 1/44 eyes (supplemental table).

No cells were detected on AS-OCT imaging of eyes of children without uveitis. Following random selection for inclusion in analysis of one eye from each child, of the 12 eyes in which active inflammation was diagnosed on slit lamp examination, AS-OCT images detected inflammatory cells in all but one (table 1). Of the 7 eyes with clinically inactive uveitis (SUN 0, no active inflammation detected on slit lamp examination), AS-OCT detected cells in two eyes. These eyes belonged to children with a known diagnosis of chronic relapsing remitting anterior uveitis.

The negative predictive value of AS-OCT manual image cell count for the diagnosis of active inflammation ('ruling out' inflammation) across the 26 children with and without uveitis was 92% (95% CI 65%-99%) (table 1).

Table 1. Diagnostic accuracy of anterior segment OCT versus slit lamp examination

	Positive OCT	Negative OCT	Total
Active inflammation on slit lamp	11	**1**	12
No active inflammation on slit lamp	**2**	12	14
Total	13	13	26

Sensitivity: 91·7; 95% Confidence Interval 61·5 to 99·8
Specificity: 85·7; 95% CI 57·2 to 98·2
Positive Likelihood ratio: 6·4, 95% CI 1·8 to 23·4
Negative Likelihood ratio: 0·1; 95% CI 0·01 to 0·6
Positive Predictive Value: 84·6; 95% CI 60·1 to 92·3
Negative Predictive Value: 92·3; 95% CI 64·5 to 98·8
Accuracy: 88·5; 95% CI 69·9 to 97·6

Correlation of AS-OCT cell count and clinical assessment of inflammation

On multilevel regression modelling (thus enabling use of both eyes for each child with adjustment for clustering at participant level) there was good positive correlation between clinical assessment and image based cell count (coefficient 3·3, 95% CI 1·3 – 5·2, R^2=0·63, p=0·002) (figure 2).

DISCUSSION

From this study, we report that acquisition of anterior chamber images in children is feasible and acceptable to children and their families. Manual analysis of images is open to inter- and intra-observer variability, but acquired images can be used to diagnose active inflammation with high levels of sensitivity and specificity.

The limitations of this study include the small sample size, and the setting within a quaternary care centre. As such, study findings cannot necessarily be extrapolated to the wider population of children at risk of uveitis. However, image acquisition was uniformly viewed to be acceptable by the children undergoing imaging and their families. The same is likely to be true for the wider population. Acceptability of AS-OCT as a diagnostic intervention has in this study been assessed through the narrow window of the “affective attitude” of children and families towards image acquisition. A more robust and multi-faceted approach to determining the acceptability of this novel diagnostic modality would include measurement of the perceived effectiveness, comparison to existing modalities, opportunity costs, as well as burden.(9) The latter has been indirectly captured within our study through examination of the duration of image acquisition, and it is reasonable to presume that the other perceived or experienced aspects of acceptability have influenced

participant's scores. This study is able to report with confidence that the majority of children and families have a strongly positive experience of AS-OCT image acquisition within the settings of a feasibility study, which speaks towards acceptability within the broader context of clinical practice.

Poor vision has a significant negative impact on a child and the adult they become.(2, 10) The strongest predictor of poor visual outcome for children with JIA associated uveitis is the presence of established eye complications at diagnosis.(11) Early diagnosis, before uncontrolled inflammation has led to structural sequelae, is key to avoiding life-changing visual disability in children at risk. The current diagnostic tool, slit lamp assessment with quantification of inflammation using the international SUN scale, is subjective, semi-quantitative with wide interobserver variability, and has not been validated for use in children.(12) Images such as those successfully acquired in our study are suitable for automated assessment of cell count. Automated analysis would enable an objective, sensitive measure of the presence and degree of inflammation.(7) Laser based flare measuring machines have been used to monitor childhood uveitis through objective quantification of the degree of protein in anterior ocular chamber aqueous fluid. These instruments have not been widely adapted for clinical use because of the time burden of acquisition, cost, and poor clinical utility in other disease areas.(11) Conversely, similarly priced OCT machines have been widely adopted in secondary and primary care setting, and across high street opticians, due to proven clinical utility in a wide variety of common adult eye conditions.(13) This wide adoption would support the future implementation of imaging based uveitis surveillance, and imaging augmented disease monitoring, using images acquired in the community. This would be particularly desirable over the current situation where uveitis surveillance typically

necessitates examination every three months within a paediatric eye centre. These centres may be geographically distant from the child's home,(14) and there is growing concern about insufficient workforce in paediatric ophthalmology.(15) Recent attempts to build OCT machines which patients can use to self-image have been successful,(16) and pave the way for home based telemedicine consultations. OCT based assessments have the additional advantage, over slit lap examination, of enabling the assessor to sit at some distance from the patient, lowering the risk of disease transmission in the COVID-19 era.

AS-OCT correlates reasonably well with slit lamp examination, but further work is needed to refine AS-OCT imaging protocols (particularly for younger children) across the different available OCT machines, to automate image analysis in order to further remove variability, and to understand the predictive power of imaging for longer term outcomes of interest to clinicians and patients, similar to the work undertaken to demonstrate the utility of MRI measures as early independent predictors of progression in structural joint damage on X-ray. This will be particularly key for those children with inflammation detectable on OCT who appear 'quiet' on slit lamp examination. Remission is defined as the cessation of a disease or symptoms for a defined period of time. Uveitis specialists now face a challenge familiar to other rheumatologists, that of defining disease cessation, which will require prospective studies able to examine long term outcomes for children stratified using varying definitions of remission.

Research into outcomes for children with JIA associated uveitis, or uveitis associated with other autoimmune or autoinflammatory disorders, requires reproducible and child appropriate outcome measures. Imaging based metrics for uveitis holds the

promise of providing sensitive, robust, validated measurement of disease status which, alongside standardised datasets and patient centred metrics, can also improve service provision, prognostication and precision in disease management for affected or at risk children. Posterior segment OCT imaging for adult retinal disease was initially undertaken only in specialist eye centres, then rapidly adopted across primary care settings, with subsequent automation of analysis across the different imaging platforms.(6) A similar trajectory for AS-OCT assessment of inflammation will require validation studies to refine acquisition protocols and implement automation of image assessment. These studies will establish the most cost effective and clinically effective use of AS-OCT imaging (cross-platform image acquisition and image analysis) for childhood uveitis, when compared to routine clinical examination. Imaging based uveitis surveillance may provide community based, objective, sensitive, telemedicine care processes for children with JIA.

Acknowledgments: We thank Elizabeth Graham, Harry Petrushkin, Sandrine Lacassagne, and Reshma Pattani for their support with this work.

Financial Support: S Akbarali was supported by a grant from the Great Ormond Street Hospital Charity (Ref V0419). AL Solebo is supported by an NIHR Clinician Scientist award (CS-2018-18-ST2-005). JS Rahi is supported in part by the National Institute for Health Research Biomedical Research Centre (NIHR BRC) based at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, and an NIHR Senior Investigator award. This work was undertaken at UCL Institute of Child Health / Great Ormond Street Hospital for children which received a

proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Declaration of interests

No conflicting relationship exists for any author.

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ALS conceptualised and ALS, AD, XL and JSR designed the study. ALS, SA, CE contributed to data collection. ALS, SA, KP and KE undertook data analysis. ALS and SA drafted the manuscript. All authors were involved in manuscript refinement and all authors approved the final version of the manuscript.

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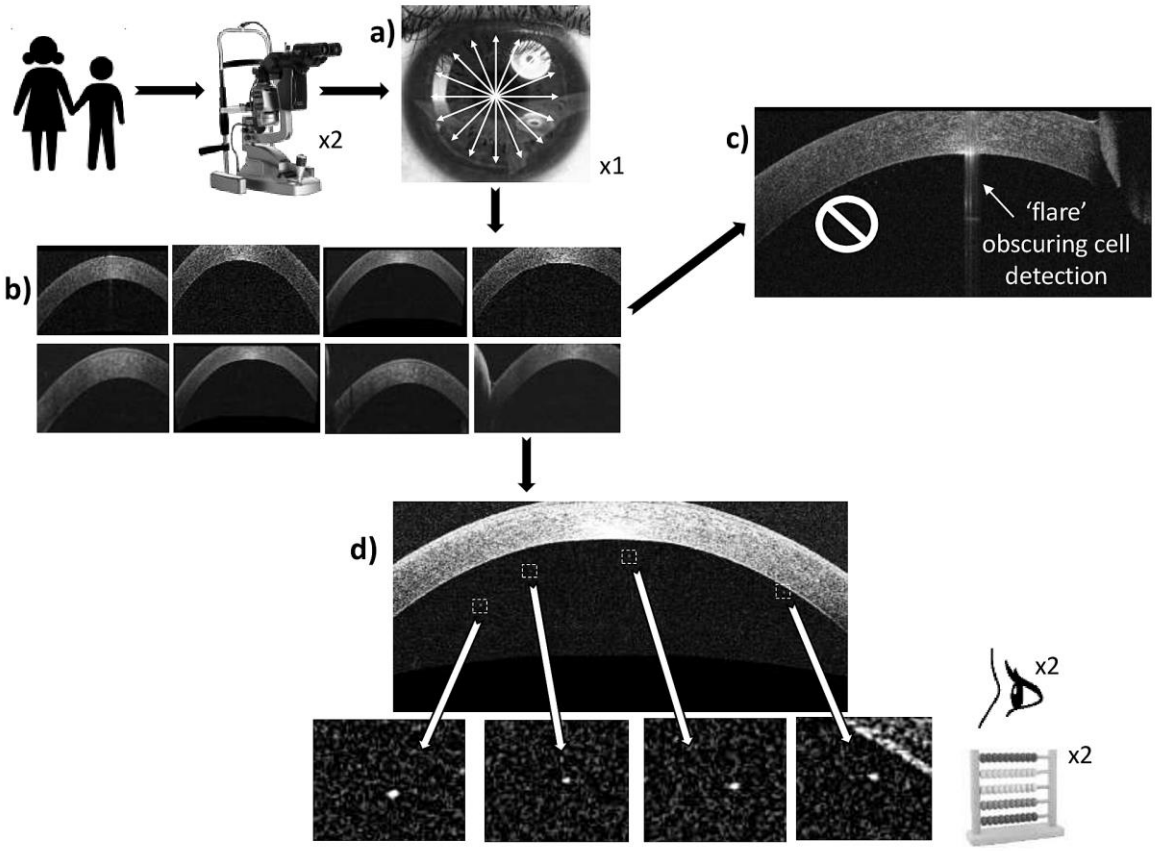
Figure 1. Image acquisition and analysis



Following clinical examination and image acquisition, cross sectional images underwent magnification and analysis

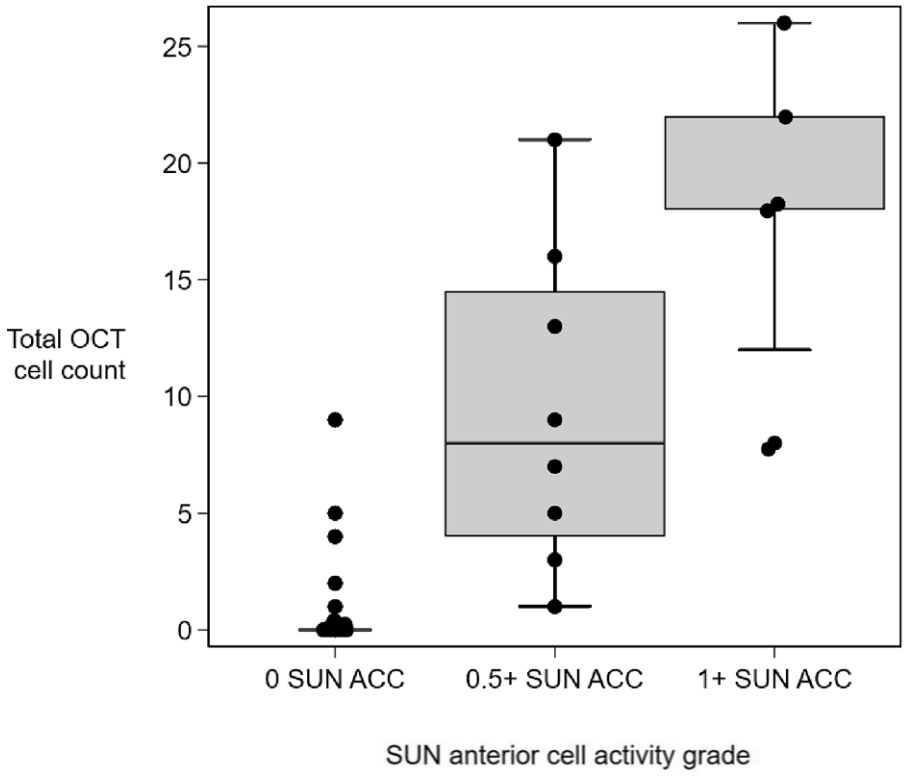
a) 1 set of 8 cross sectional images acquired from each eye

b) Image sets downloaded to analysis programme and reviewed for quality

c) Images with 'flare' discarded

d) Manual analysis of good quality images: 44 eyes from 26 children with full set of 8 good quality images, 8 eyes from 8 children with incomplete sets (range 1 – 6 good quality images acquired per eye)

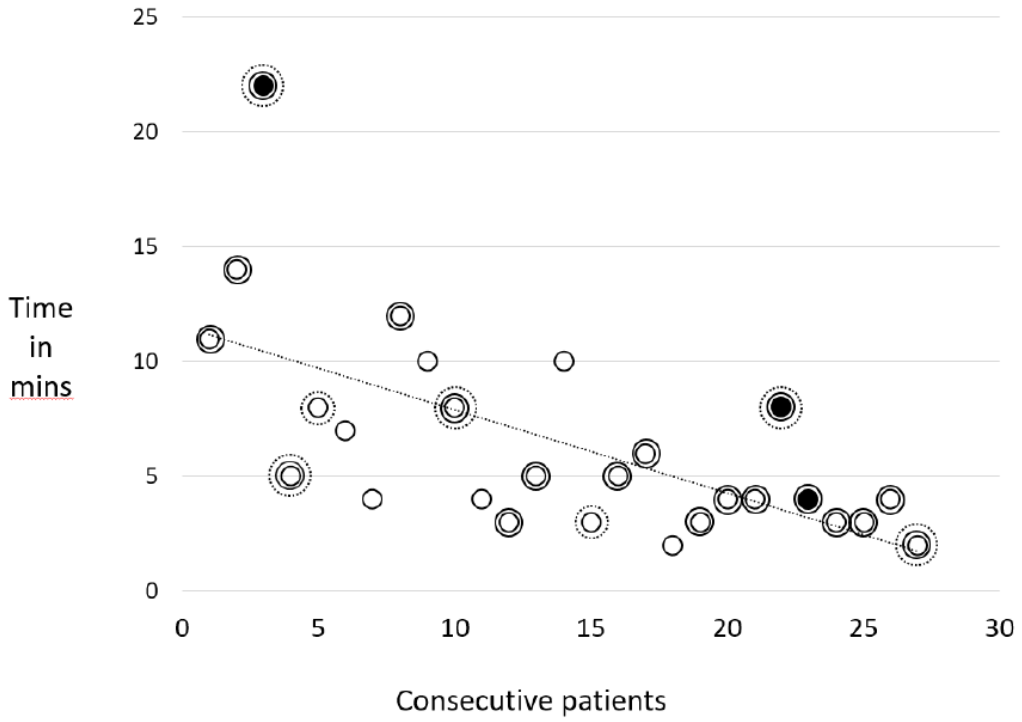
Figure 2. Correlation between slit lamp and AS-OCT quantification of inflammation



All 44 eyes of 26 children with full set of 8 images included in the diagram.

All eyes of children in the 'control' group (free of uveitis) had zero cells on AS-OCT imaging.

412 **Supplemental figure S1**



413

414 Filled circles represent children aged under 6 years

415 Double solid circles indicate successful capture of full set of 8 analysable images

416 from both eyes.

417 Dashed circle indicates child from the ‘control’ group (no uveitis)

418 Children were permitted to rest in between acquisition of images from each eye: rest

419 time was included in total duration time of scan

420

Supplemental tables: Intraobserver agreement for clinical examination and imaging analysis

Supplemental Table S1. Agreement between slit lamp examiners (eye level)

Slit lamp agreement		**Examiner two**		
		Inactive (SUN 0)	*Active (≥ SUN 0.5+)*	*Total*
Examiner one	*Inactive (SUN 0)*	29 eyes	1 eye	30 eyes
	Active (≥ SUN 0.5+)	0 eye	14 eyes	14 eyes
	Total	29 eye	15 eyes	44 eyes

Supplemental Table S2. Agreement between OCT assessors (eye level)

OCT count agreement		**2nd observer (more than one individual)**		
		Inactive (no cells)	*Active*	*Total*
Observer one (one individual)	*Inactive (no cells)*	20 eyes	5 eyes	25 eyes
	Active	1 eye	18 eyes	19 eyes
	Total	21 eyes	23 eyes	44 eyes

Supplemental Table S3. Agreement between OCT assessors (scan level)

OCT count agreement		**2nd observer (more than one individual)**		
		Inactive (no cells)	*Active*	*Total*
Observer one (one individual)	*Inactive (no cells)*	265	11	276
	Active	14	87	101
	Total	279	98	377