7/14/2022 04:10 pm

Inflammatory & Infectious Diseases Symposium

Biomarkers in the Vitreous Humor Correlate With Alzheimer's Disease and Chronic Traumatic Encephalopathy in Postmortem Eyes and Brain

- Manju Subramanian, MD
- Viha Vig, B A in Biochemistry & Molecular Biology
- Fatima Tuz-Zahra
- Thor Stein, MD, PhD

Objective:
To Examine Known Biomarkers for Neurodegenerative Disease in Postmortem Vitreous Humor and Correlate Them with Neuropathological Diagnosis and Cortical Brain Tissue Biomarkers from Donated Eyes and Their Corresponding Brains.

Purpose:
The eye provides a direct window to display neuro-retinal disease and the interconnections between the eye and brain may elucidate common features of both neurological and eye diseases. This study sought to examine vitreous levels of biomarkers in postmortem eyes and brains of those with Alzheimer's Disease (AD), Chronic Traumatic Encephalopathy (CTE) of brains from professional athletes, and healthy controls.

Methods:
In this exploratory, retrospective, validation study, we examined 43 donated postmortem eyes and corresponding brains, with pathological diagnoses of AD, CTE, both AD + CTE, and healthy controls. Neuropathological diagnosis of brain samples were conducted by a neuropathologist. Amyloid-beta (Aβ), total and phosphorylated tau (tTau, pTau), neurofilament light chain (NfL), and eotaxin-1 was quantitatively measured by Meso Scale Discovery immunoassay in both the vitreous and cortical tissue. Non-parametric ANOVA - Kruskall-Wallis Rank sum test and Wilcoxon rank tests were used to determine if vitreous biomarker levels were significantly associated with pathological diagnosis, ADNC, and CTE Staging. Spearman's rank correlation was used to compare biomarker levels in vitreous and cortical tissue.

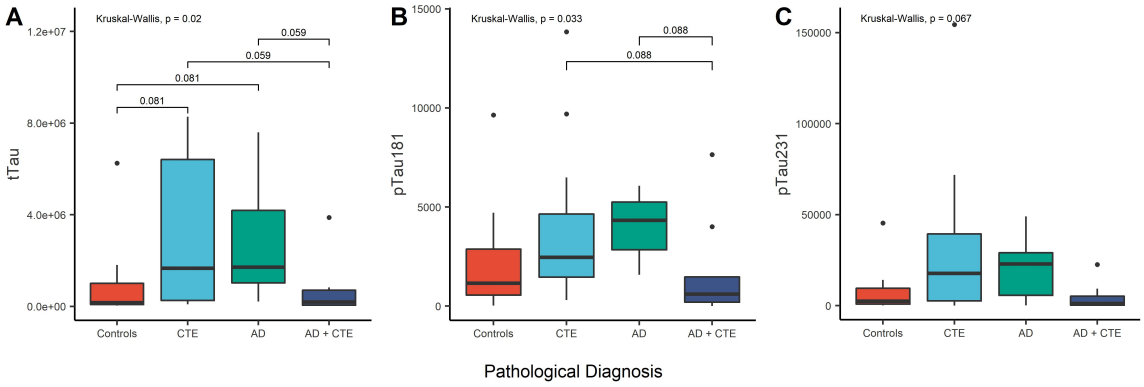
Results:
Vitreous levels of tTau (p=0.016), pTau-181 (p=0.0064), and pTau-231 (p=0.042) were significantly and strongly associated with pathological brain diagnoses. In pairwise comparisons, significant differences in biomarker levels were found for tTau in AD+CTE (n=9) vs CTE (n=15) (p=0.048) and AD+CTE vs AD (n=7) (p=0.048). Vitreous and cortical tissue levels of eotaxin-1 (p=0.013, n=29, r=-0.45) and t-Tau (p=<0.001, n= 39, r=0.61) were significantly correlated. NfL (p=0.017, n=33) and Abeta-42 (p=0.057, n=40) in the vitreous were also strongly associated with CTE Staging.

Conclusion:
Biomarkers with known associations to neurodegenerative diseases (tTau, pTau-181, and pTau-231) in postmortem vitreous humor significantly correlate with confirmed AD and CTE pathology in post-mortem brains, and vitreous NfL and Abeta-42 correlate strongly with the various stages of CTE. Additionally, vitreous humor and cortical tissue levels of tTau and eotaxin-1 showed significant associations. This study is the first to correlate proteins in the eye, known for neurodegnerative diseases, with CTE from the brains of professional athletes, and we also validate prior reports by our group that protein biomarkers in the vitreous humor have significant associations with cognitive function, lending further credence that the eye may serve as a proxy for neuropathological diseases with potential for diagnostic capabilities and prognostication.

IRB APPROVAL Yes

Pathological Diagnosis vs Vitreous Biomarker Levels			
Protein	**Sample size (n)**	**P-value**	**Spearman's Rank Correlation**
pTau181	41	0.0064	-
tTau	41	0.016	-
pTau231	41	0.042	-
tTau	pairwise comparison: AD+CTE (n=9) vs CTE (n=15)	0.048	-
tTau	pairwise comparison: AD+CTE (n=9) vs AD (n=7)	0.048	-
CTE Staging vs Vitreous Biomarker Levels			
NfL	33	0.017	-
Vitreous vs Cortical Biomarker Levels			
tTau	39	0.0001	0.61
Eotaxin-1	32	0.013	-0.45

Vitreous Biomarker Association with Neurodegeneration



Vitreous Tau associations with Neuropathological Diagnoses

7/14/2022 04:16 pm

Inflammatory & Infectious Diseases Symposium

Association of OCT Choroidal Thickness Maps and Automated Fixed-Depth Intensity Maps With Disease Activity in Birdshot Chorioretinopathy

- Keirnan Willett, MD
- Wendy Smith, MD

Objective:
Are choroidal thickness maps useful for monitoring disease activity in birdshot chorioretinopathy?

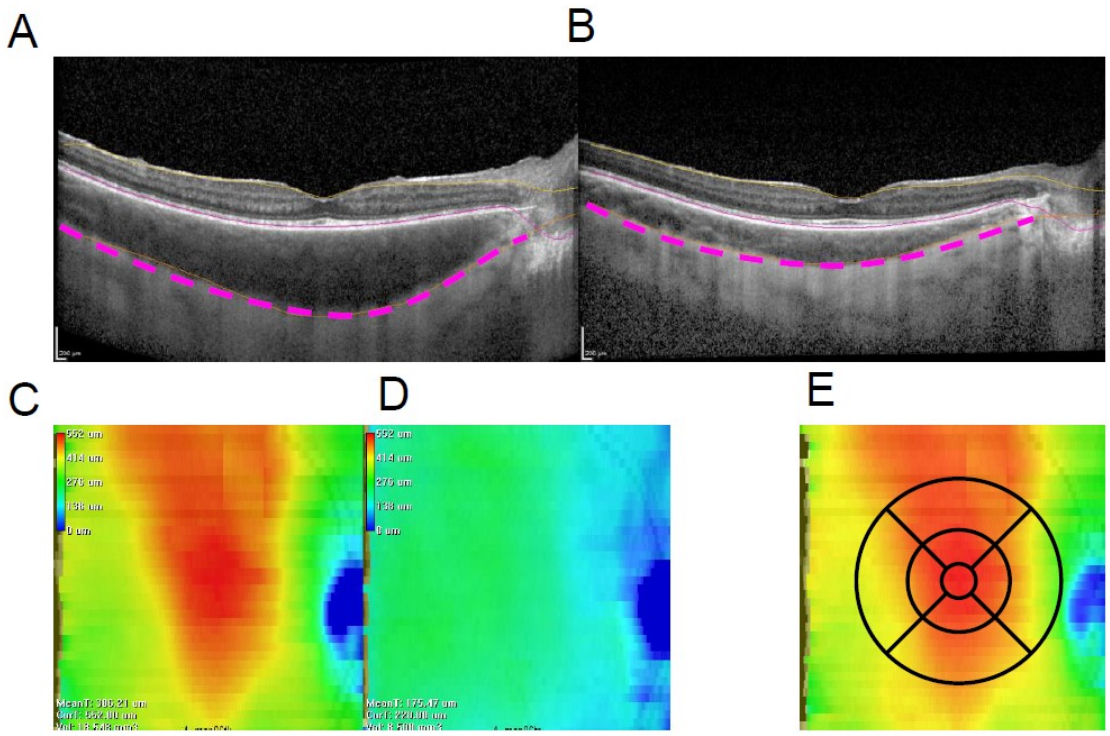
Purpose:
The aim of this study is to broaden the application of optical coherence tomography (OCT) to management of birdshot chorioretinopathy (BCR). En face maps of the choroidal thickness are assessed to see if they offer improved diagnostic information relative to center point choroidal thickness measurements which have been previously reported.

Methods:
Sequential cases of BCR were identified retrospectively from an academic referral uveitis practice and enhanced depth imaging (EDI) OCT scans were obtained. Conventional center point thickness was then compared to manually defined choroidal thickness maps as well as fixed depth pixel intensity maps posterior to the retinal pigment epitheliµm (RPE). Comparisons were made between timepoints of active and inactive inflammation based on overall clinical assessment.

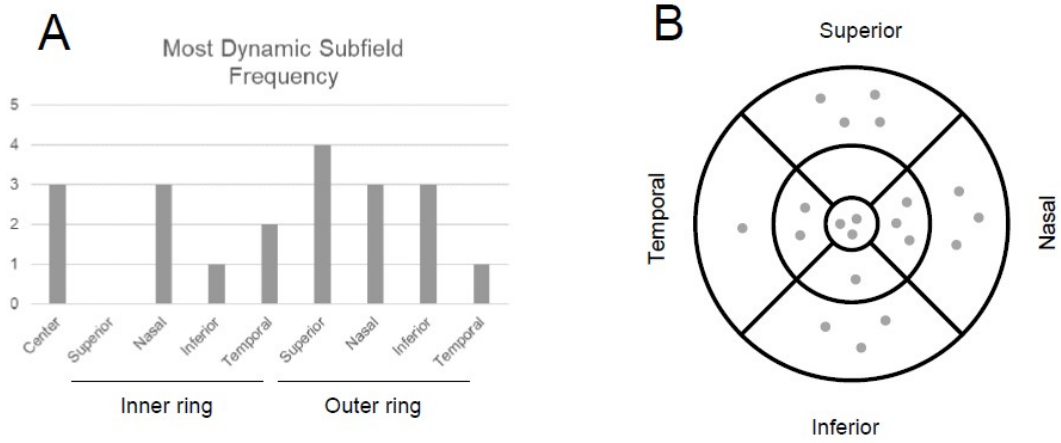
Results:
Twenty eyes of ten patients met inclusion criteria. The mean center point choroidal thickness was 267.60 (SD 123.91) and 198.95 (SD 108.13) µm at active and inactive timepoints respectively, p = 0.07. After selecting the ETDRS subfield with the greatest change between timepoints for each case, mean choroidal thickness was 308.04 (SD 127.79) µm with active inflammation versus 210.83 (SD 100.94) µm during quiescence (p=0.011). The mean volume of the outer ring of the 6mm ETDRS grid, the total volume of the ETDRS grid and the most dynamic ETDRS subfield, also were statistically significantly greater with active inflammation. Fixed depth pixel intensity maps correlated well with manually segmented choroidal thickness maps.

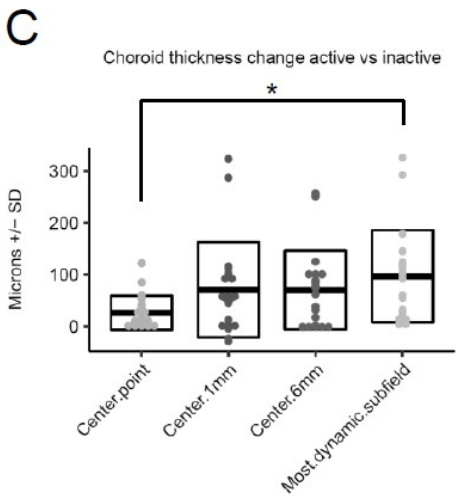
Conclusion:
Evaluation of the choroidal thickness beyond the central fovea may be a helpful imaging biomarker in BCR. Fixed depth pixel intensity projection maps may provide a way to estimate choroidal thickness with minimal manual image processing.

IRB APPROVAL No - exempt



Choroid thickness by OCT measurement was thinner with inactive disease.





Maximal changes in choroid thickness were often outside the center point.

7/14/2022 04:20 pm

Inflammatory & Infectious Diseases Symposium

Efficacy of Suprachoroidal Triamcinolone Acetonide Injectable Suspension in the Treatment of Macular Edema in Patients With Chronic Uveitis

- Christopher Henry, MD
- barry kapik, MS
- Thomas Ciulla, MD, MBA, FASRS

Objective:
This post-hoc analysis evaluated outcomes following treatment with triamcinolone acetonide injectable suspension, for suprachoroidal use in patients with macular edema associated with chronic uveitis.

Purpose:
Safety and efficacy of triamcinolone acetonide injectable suspension, for suprachoroidal use (SCS-TA) in the treatment of macular edema (ME) associated with noninfectious uveitis (NIU) was previously demonstrated in PEACHTREE. This post-hoc analysis of PEACHTREE data evaluated outcomes in a subset of patients with chronic uveitis (persistent uveitis with relapse in <3 months after discontinuing prior treatment).

Methods:
In PEACHTREE, subjects with ME secondary to NIU (N=160) were randomized 3:2 to receive a suprachoroidal injection of SCS-TA (4 mg) or a sham procedure in the study eye at baseline and Week 12. Anatomical, visual and safety outcomes were evaluated over 24 weeks. In this post-hoc analysis, BCVA (EDTRS letters) and CST (µm) were assessed in SCS-TA treated subjects characterized as having chronic uveitis at baseline. Time to rescue in these subjects compared to control subjects was also evaluated. Changes from baseline for BCVA and CST at each visit were analyzed by t-test while any between treatment differences in time to rescue were analyzed using Kaplan-Meier estimates (Log-rank test).

Results:
At baseline, 60 subjects treated with SCS-TA were characterized as having chronic uveitis. Mean age of SCS-TA subjects in this cohort was 49.9 years, the majority were female, and mean time since diagnosis was 188.1 days. Mean (SE) BCVA letters and CST (µm) at baseline were 54.0 (1.86) and 492.7 (19.88), respectively. Mean (SE) BCVA letter gains were 8.8 (1.18), 10.6 (1.35), 10.9 (1.59), 12.1 (1.72), 12.0 (1.69) and 12.1 (1.89) at Week 4, 8, 12, 16, 20, and 24, respectively (P<0.001 vs baseline at all visits). Similarly, mean (SE) reductions in CST (µm) of -158.7 (19.39), -150.5 (21.67), -135.4 (22.32), -174.3 (22.55), -167.4 (22.18), and -153.5 (22.58) were observed at these visits (P<0.001 vs baseline at all visits). Of SCS-TA treated subjects with chronic uveitis, 16.7% (10/60) required rescue compared to 65.9% (27/41) of control subjects with chronic uveitis. Median time to rescue was 139 days for control subjects and was not estimable in SCS-TA treated subjects (P<0.001).

Conclusion:
Consistent with the full dataset, in this post-hoc analysis of the pivotal Phase 3 data specific to subjects with chronic uveitis at baseline, SCS-TA was similarly effective in improving visual and anatomical outcomes in the treatment of ME associated with NIU. Few SCS-TA treated subjects required rescue as compared to control.

IRB APPROVAL Yes

7/14/2022 04:24 pm

Inflammatory & Infectious Diseases Symposium

Suprachoroidal Triamcinolone Acetonide Injectable Suspension for Macular Edema Associated With Uveitis: Integrated Analysis of 2 Clinical Trials

- Steven Yeh, MD
- Christopher Henry, MD
- barry kapik, MS
- Thomas Ciulla, MD, MBA, FASRS

Objective:
This research study evaluates the efficacy and safety of triamcinolone acetonide injectable suspension for suprachoroidal use across two Phase 3 clinical studies.

Purpose:
Triamcinolone acetonide injectable suspension, for suprachoroidal use (SCS-TA) provides targeted drug delivery to the choroid and retina while minimizing steroid exposure in nontarget tissues. This integrated analysis evaluated SCS-TA for the treatment of macular edema (ME) secondary to noninfectious uveitis (NIU) across two studies.

Methods:
Data from a randomized, double-masked, sham-controlled trial (PEACHTREE) and an open-label trial (AZALEA) were pooled. Only those subjects with ME secondary to NIU defined by a central subfield retinal thickness (CST) ≥300 µm with fluid and a best-corrected visual acuity (BCVA) of ≥5 and ≤70 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in the study eye at baseline were included in the analysis. In both studies, subjects received SCS-TA at baseline and Week 12 and were followed every 4 weeks for 24 weeks. Control subjects received a sham procedure at baseline and Week 12. Outcomes included BCVA, CST, anterior chamber (AC) cells, AC flare, vitreous haze (VH) and adverse events (AEs).

Results:
The integrated population included 95 subjects (PEACHTREE 88; AZALEA 7). Increase from baseline in BCVA was greater with SCS-TA vs control with a mean difference of 10.7 letters at Week 24 (P<0.001 for all visits). Proportions of subjects achieving a mean ≥15 letters gain were greater with SCS-TA vs control (47.4% vs 16.7% at Week 24; P<0.001 for all visits). Reduction in CST was greater and more subjects achieved a CST <300 µm with SCS-TA vs control (P<0.001 for all visits). In subjects with baseline inflammation, 72.2%, 71.1% and 72.0% in the SCS-TA group vs 13.6%, 20.0% and 19.0% in the control group achieved resolution of AC cells, flare and VH at Week 24 (all P<0.01). Rescue therapy was required by 12.6% and 73.3% of subjects in the SCS-TA and control groups, respectively. AEs were mostly mild and no treatment-related serious AEs were reported. Overall, incidence of elevated intraocular pressure (IOP) was 20% and 15% in the SCS-TA and control groups (7.4% vs 0% at time of procedure; 12.6% vs 15% post-procedure, control IOP events occurred post rescue). Cataract rates were 7.4% and 6.7% for SCS-TA and control respectively.

Conclusion:
In this integrated analysis of two Phase 3 clinical trials, SCS-TA was confirmed to be effective and well-tolerated in the treatment of ME associated with NIU.

IRB APPROVAL Yes

7/14/2022 04:37 pm

Inflammatory & Infectious Diseases Symposium

Ultra-Widefield Fluorescein Angiography and OCT Findings in Children and Young Adults With Autosomal Dominant Neovascular Inflammatory VitreoretinopathyW

- Arjun Sood, MD
- Sheila Angeles-Han, MD, MSc
- Cameron Sapp, BS
- Jared Ebert, MD
- Sumit Sharma, MD
- Sunil Srivastava, MD

Objective:
We report multimodal imaging findings in children and young adults with ADNIV.

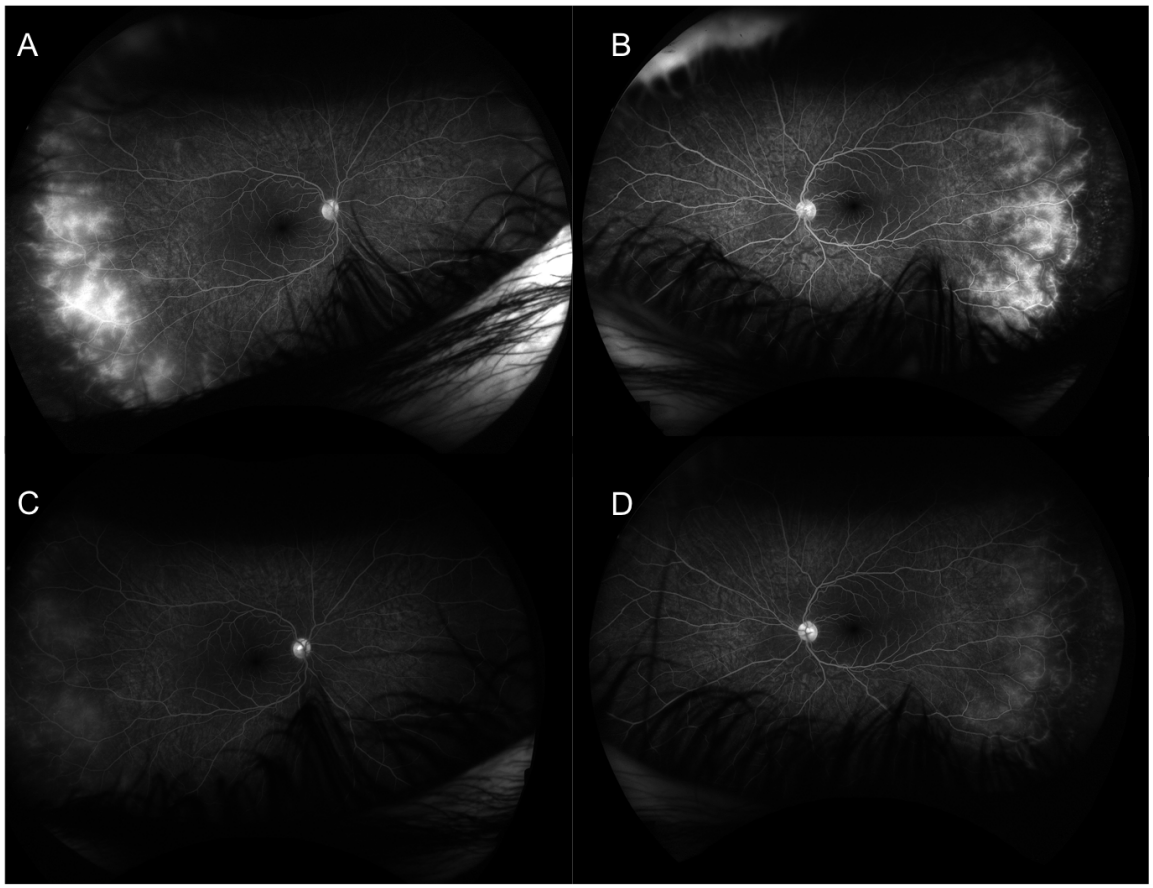
Purpose:
Autosomal Dominant Neovascular Inflammatory Vitreoretinopathy (ADNIV) is a rare auto-immune condition characterized by the triad of uveitis, retinal degeneration and neovascularization (NV) that leads to permanent blindness. There is limited data on the multimodal imaging features of this disease. In this study, we present ultra-widefield fluorescein angiography (UWFA) and OCT findings in children and young adults with ADNIV.

Methods:
Retrospective consecutive case series. Patients with CAPN5 gene mutation (c.731 T>C, p.Leu244Pro) and diagnosis of ADNIV were included. Electronic medical records were reviewed for abnormal findings on UWFA and OCT.

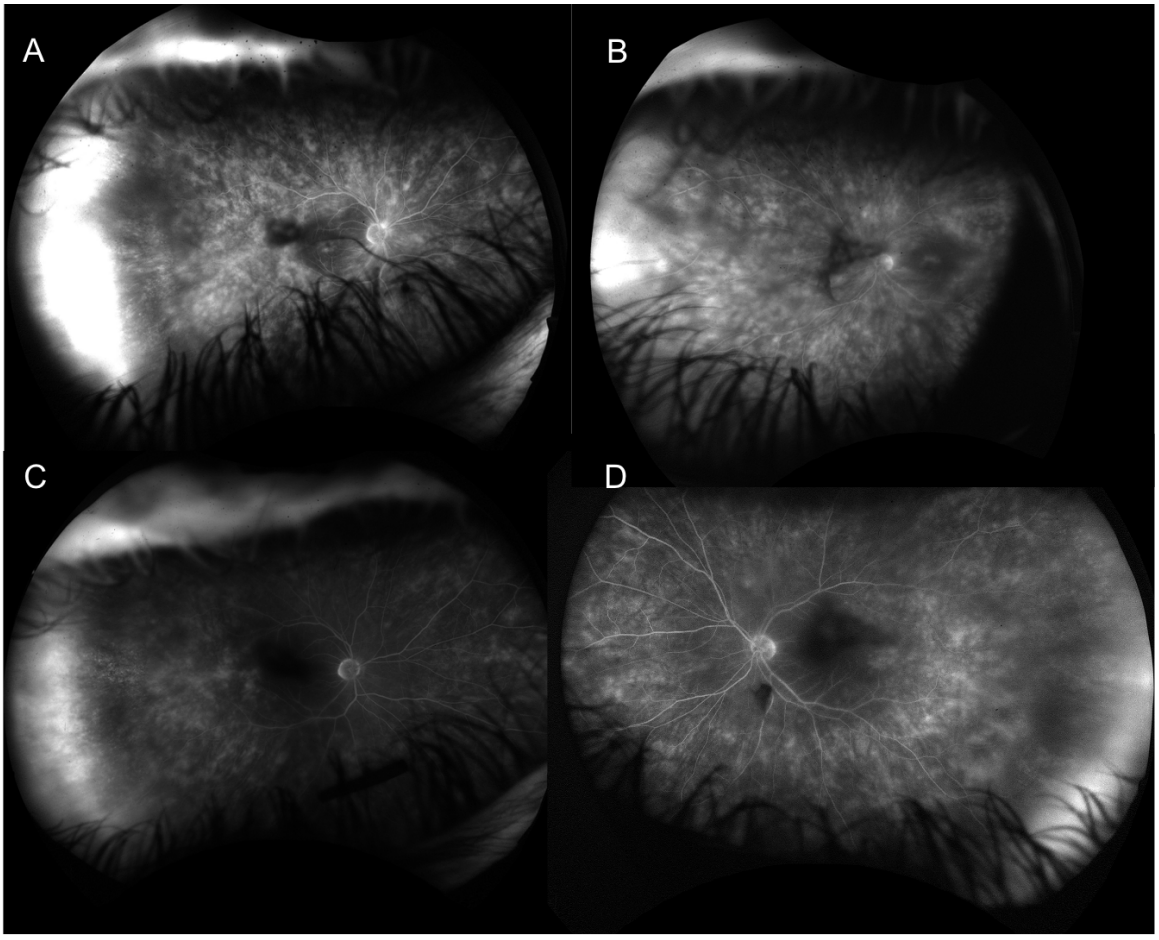
Results:
A total of 14 eyes from 7 ADNIV patients (5 female; mean age 15 years, range 10-24 years) were included. All patients underwent UWFA and OCT testing. Four patients were asymptomatic at presentation. On UWFA imaging, 14 eyes (100%) demonstrated retinal vascular leakage, 12 eyes (86%) showed peripheral non-perfusion/ischemia, and 6 eyes (43%) showed neovascularization. On OCT imaging, 8 eyes (57%) demonstrated macular edema. Patients were treated with oral prednisone and/or local steroid injections and showed improvement in retinal vascular leakage (14/14 eyes) and macular edema (6/8 eyes; 75%). Patients with neovascularization at presentation were also treated with anti-VEGF therapy with regression of retinopathy (6/6 eyes).

Conclusion:
Occult retinal vasculitis is an under-recognized feature in patients with ADNIV and present in even asymptomatic children. Chronic and un-treated inflammation leads to ischemia, neovascularization, and permanent vision loss. Early identification using UWFA will lead to prompt intervention with anti-VEGF therapy, laser and local/systemic immunosuppression, which may improve outcomes and alter the natural history of eventual blindness.

IRB APPROVAL Yes



Retinal vascular leakage before (A-B) and after treatment (C-D)



Retinal vascular leakage and NV before (A-B) and after treatment (C-D)

7/14/2022 04:41 pm

Inflammatory & Infectious Diseases Symposium

Heterogeneous Presentations of De Novo and Recurrent Uveitis After COVID-19 Vaccination: Multicenter Report

- Sruthi Arepalli, MD
- Laura Kopplin, MD
- Edmund Tsui, MD
- Daniel Brill, MD
- Veena Raiji, MD, MPH
- Parisa Emami Naeini, MD, MPH
- Akshay Thomas, MD, MS

Objective:
To discuss the heterogeneous presentation of de-novo or recurrence of pre-existing uveitis following COVID-19 vaccination and report on the low rate of these occurences.

Purpose:
The COVID-19 vaccine is necessary to reduce healthcare burdens, but rarely, uveitis after the vaccine has been reported, possibly due to triggering an immune response. It is essential to document the heterogeneous presentation of uveitis and low overall rate of temporally associated flares.

Methods:
A retrospective chart review of six retina and uveitis centers centers (TNR, UCLA, UC Davis, UW-Madison, Mass Eye and Ear, Cook County) was completed from 12/1/20 to 12/1/21. Patients must have had at least one COVID-19 vaccination to be included as a control group to assess baseline uveitis flare rates in both new uveitis cases and established uveitis patients. At least one COVID-19 vaccination and a documented uveitis flare within 40 days following the vaccination were required in order to be included in the de novo or recurrent uveitis groups. In total, 323 patients were analyzed. Patients were designated as de-novo if they had no uveitis history or recurrent if their prior uveitis was quiescent before vaccination.

Results:
In total, 323 patients were included. Of these, 37 (12%) developed uveitis, and categorized as de-novo (22, 7%) or recurrent (15, 5%). The remaining patients served as controls to estimate inflammation rates. To assess the rate of new uveitis temporally associated with vaccination a group of new uveitis referrals to 1 center were analyzed over a 6-month period, yielding 52 double-vaccinated patients with 7 (13%) symptomatic within 40 days. To estimate inflammation rate in established patients, the number of patients who flared in 40 days of vaccination from 2 centers were compared to all established patients from these centers who did not flare within 40 days. This resulted in 11 (5%) who flared compared to 234 established patients who did not.

22 patients (36 eyes) had de-novo inflammation after Pfizer (11, 50%) or Moderna (10, 45%). The mean age was 51 years. Symptom onset averaged 10 days after vaccination. 9 (41%) flared after the first vaccine, while 5 additionally flared after the second. Anterior uveitis was the most common (9 eyes, 25%) and retinal vasculitis was rare, but there was a myriad of phenotypes. (Table 1, Figure 1) 35 eyes (97%) obtained quiescence.

15 patients (17 eyes) presented with uveitis recurrence after Pfizer (11, 73%), Moderna (3, 20%) or AstraZeneca (1, 7%). The mean age was 55 years. Disease quiescence averaged 104 weeks prior to vaccination. Symptom onset occurred on average 12 days after vaccination. 12 eyes (71%) developed anterior uveitis. (Table 1) In all but 2 eyes, inflammation mimicked prior inflammation. Quiescence was obtained in 16 (94%) eyes.

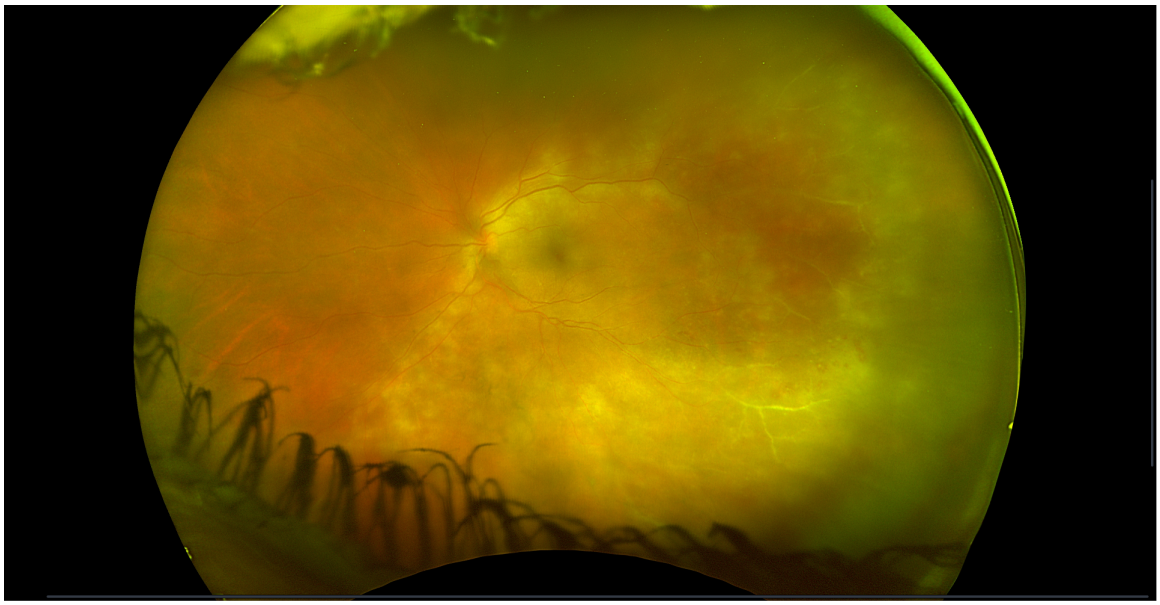
Conclusion:
Uveitis following COVID-19 vaccination is rare and causality is difficult to assess, but many heterogenous presentations exist. In a few patients, flares occured after both vaccines hinting a stronger relationship. Most patients obtained quiescence at final follow-up.

IRB APPROVAL Yes

Table 1: Presentation of inflammation in de-novo or recurrent cases following COVID-19 Vaccination

Inflammation Category	**De- Novo (N=36 Eyes)**	**Pre-Existing (N= 17 Eyes)**
Anterior	9 (25%)	12 (7%)
Intermediate	4 (11%)	1 (6%)
Posterior	2 (6%)	0 (0%)
Intermediate and Posterior	2 (6%)	0 (0%)
Panueveitis	3 (8%)	0 (%)
Scleritis	6 (17%)	3 (18%)
Retinal vasculitis	2 (6%)	0 (0%)
Cystoid macular edema	2 (6%)	0 (0%)
Optic nerve edema	3 (8%)	0 (0%)
Optic neuritis	2 (6%)	0 (0%)
Peripheral ulcerative keratitis	0 (0%)	1 (6%)

The presentations of uveitis (by eyes) for de-novo or recurrent uveitis



Panuveitis and sheathing after vaccine which improved after oral steroids

7/14/2022 04:47 pm

Inflammatory & Infectious Diseases Symposium

Ocular Involvement in Candidemia Diagnosed by T2 vs Blood Culture With Recommendations on Screening for Endogenous Candida Endophthalmitis

- John Mason, MD
- Jason Crosson, MD
- John Luckett, MD

Objective:
Are blood cultures or T2 test better for detecting Candidemia with ocular involvement , and does this have implications for screening for Endogenous Candida Endophthalmitis ?

Purpose:
To evaluate ocular involvement in Candidemia diagnosed by T2 vs blood cultures, and recommendations on screening for Endogenous Candida Endophthalmitis

Methods:
Retrospective chart review of 166 consecutive patients admitted to UAB hospital from January1, 2019 - December 31,2019 with a diagnosis of Candida sepsis . 97/166 met inclusion criteria of a positive T2 or blood culture for Candida , and a dilated ocular exam . Main outcome measure was Candida ocular involvement , and secondary outcomes were symptoms and visual acuity related to ocular involvement. Results were analyzed using Fischer's exact test .

Results:
Mean age of 97 patients was 52.7 , with almost equal male (48) to female (49) ratio. Blood cultures were performed on 97/97 and T2 on 78/97 patients. Blood cultures were positive on 47/97(48 %) and T2 on 69/78(88%). 44.3% of patients were deceased at chart review. Ocular involvement was found in 6/97 (6.2%) patients consisting of 5/97 with chorioretinitis and 1/97 with Endophthalmitis. There was no statistical significance when comparing eye exam findings to age, sex , symptoms, Candida species , or method of diagnosis ($P > 0.05$). When comparing an eye exam to vision , there was a higher rate of vision >20/30 in ocular involved patients ($P= 0.0146$) . Only 1/6 patients with ocular involvement had vision < 20/30 .

Conclusion:
The T2 test is more sensitive than blood cultures in detecting candidemia , while the incidence of ocular candidiasis , and especially Endophthalmitis, is low . Screening all candidemia patients is of low value, and our results suggest screening those patients that are non verbal or symptomatic.

IRB APPROVAL Yes