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## Association between Pseudodrusen and Delayed Patchy Choroidal Filling in the Comparison of AMD Treatments Trials (CATT)

Qiang Zhou, MD<sup>1</sup>, Ebenezer Daniel, MBBS, PhD<sup>2</sup>, Juan E. Grunwald, MD<sup>2</sup>, Maureen G. Maguire, PhD<sup>2</sup>, Dina Y Gewaily, MD<sup>2,3</sup>, Daniel F. Martin, MD<sup>4</sup>, and Gui-shuang Ying, PhD<sup>2</sup> on behalf of CATT Research Group

<sup>1</sup>Department of Ophthalmology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, P. R. China

<sup>2</sup>Department of Ophthalmology, Scheie Eye Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

<sup>3</sup>Deglin and Greene Retinal Center, Philadelphia, PA, USA

<sup>4</sup>Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA

### Editor

Pseudodrusen have been identified as a strong risk factor for development of late age-related macular degeneration (AMD) (Zhou et al. 2016; Alten & Eter 2015; Chang et al. 2016) and macular atrophy (Munk et al. 2016). However, the pathophysiological mechanism for the formation of pseudodrusen and their underlying association with late AMD are mostly unknown (Alten & Eter 2015). Recent studies have found that the location of evolving pseudodrusen is related to the location of choroidal watershed zones, and that eyes with pseudodrusen have reduced choroidal thickness, choroid volume, and choriocapillaris vessel density (Alten & Eter 2015; Alten et al. 2016), suggesting that choroid hypoxia may play an important role in the pathogenesis of pseudodrusen. Delayed patchy choroidal filling (DPCF) on fluorescein angiography (FA) is a marker of decreased choroidal circulation and ischemia (Pauleikhoff et al. 1999). Using images collected from the Comparison of AMD Treatments Trials (CATT), we evaluated possible associations between pseudodrusen and DPCF.

Details for the CATT, methods for evaluating pseudodrusen and DPCF have been published previously (Zhou et al. 2016; Martin et al. 2011; Gewaily et al. 2014). In brief, the CATT enrolled 1185 participants with age 50 years or older, active choroid neovascularization, and visual acuity 20/25 to 20/320 in the study eye (one study eye per participant). The institutional review board associated with each participating center approved the protocol.

**Corresponding Author:** Gui-shuang Ying, PhD, 3535 Market Street, Suite 700, Philadelphia PA 19104, 215-615-1514 (Phone), 215-615-1531 (Fax), gsyng@mail.med.upenn.edu.

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Each participant provided written informed consent and study followed the Declaration of Helsinki.

DPCF in the study eye at baseline was evaluated using FA by 2 trained readers with the equivocal cases adjudicated by a senior grader in the CATT photograph reading center. The DPCF was deemed present if at least half a disc diameter of patchy choroidal filling was present beyond the early venous transit phase (Gewaily et al. 2014). Baseline pseudodrusen in the study eye and in the fellow eye were assessed using digital color fundus photography viewed under full color, green channel, and blue channel; red-free images; and FA (Zhou et al. 2016).

We evaluated the association between baseline pseudodrusen and DPCF in the study eye using the odds ratio (OR) and its 95% confidence interval (CI) as estimated from logistic regression models without and with adjustment for age, gender and smoking status. Because active choroidal neovascularization in the study eye could obscure the appearance of pseudodrusen and because pseudodrusen are often bilateral (Sadde et al. 2014), we evaluated the association of pseudodrusen in either eye, as well as pseudodrusen in the study eye and the fellow eye, with DPCF.

A total of 870 CATT participants with baseline images of sufficient quality for determining both pseudodrusen and DPCF were included in this analysis. Their mean (standard deviation) age was 79 (7.6) years, 541 (62.2%) were female, 88 (10.1%) were current smokers and 423 (48.6%) former smokers. At baseline, pseudodrusen were present in 168 (19.3%) study eyes, and 229 (26.3%) fellow eyes. Pseudodrusen were present in both eyes in 145 (16.7%) participants.

At baseline, DPCF was present in 68 (7.8%) study eyes. The participants with pseudodrusen in either eye had a higher proportion with DPCF in the study eye than participants without pseudodrusen (11.5% vs. 6.3%,  $P=0.01$ ). The association remained significant after adjustment by age, gender and smoking status (adjusted OR=1.95, 95% CI: 1.16 – 3.30, Table 1).

The proportion with DPCF in the study eye was higher in participants with pseudodrusen in both eyes (14.5%) or in the study eye only (13.0%) than in participants with no pseudodrusen in either eye (6.3%) or pseudodrusen in the fellow eye only (6.0%) ( $P=0.009$ , Table 1). The OR of having DPCF for participants with pseudodrusen in both eyes was 2.55 (95% CI: 1.40 – 4.64) relative to participants with no pseudodrusen in either eye.

This study found that CATT participants with baseline pseudodrusen were approximately 2 times more likely to have DPCF than participants without pseudodrusen. Because DPCF is an indicator of choroid circulation abnormalities, our results further demonstrate the association between these abnormalities and pseudodrusen. Because our study is limited by using digital fundus photographs and FA which are not optimal for determining pseudodrusen, future studies using more recently developed retinal imaging such as confocal scanning laser ophthalmoscopy, spectral-domain optical coherence tomography, or retromode imaging (Parravano et al. 2016) are needed to validate our finding. Further longitudinal study will also be necessary to determine whether choroidal ischemia and

perhaps hypoxia lead to pseudodrusen, and whether long standing retinal pigment epithelial and outer segment disease, from AMD, Sorsby's dystrophy, Lord Syndrome, and others, lead to pseudodrusen with secondary choroidal changes, or both.

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**Table 1**

Association between pseudodrusen and delayed patchy choroid filling at baseline

	N	Delayed patchy choroid filling at baseline in study eye: Yes (%)	OR (95% CI)	P-value	Adjusted OR (95% CI) <sup>§</sup>	P-value
Pseudodrusen at baseline in either eye						
No	618	39 (6.3%)	1.0		1.0	
Yes	252	29 (11.5%)	1.93 (1.17 – 3.20)	0.01	2.00 (1.17 – 3.42)	0.01
Combination of baseline pseudodrusen in study eye and fellow eye				0.009		0.01
Neither	618	39 (6.3%)	1.00		1.00	
Fellow eye only	84	5 (6.0%)	0.94 (0.36 – 2.46)		1.02 (0.38 – 2.72)	
Study eye only	23	3 (13.0%)	2.23 (0.63 – 7.82)		2.26 (0.63 – 8.03)	
Both eyes	145	21 (14.5%)	2.52 (1.43 – 4.42)		2.55 (1.40 – 4.64)	

OR = odds ratio, CI = confidence interval.

<sup>§</sup> Adjusted by age, gender and smoking status.