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Ophthalmology-Based Neuropathology Risk Factors: Diabetic Retinopathy is Associated with Deep Microinfarcts in a Community-Based Autopsy Study

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Abstract

Background: The aging eye offers unique opportunities to study and understand the aging brain, in particular related to Alzheimer's disease (AD) and dementia. However, little is known about relationships between eye diseases and dementia-related neurodegeneration.

Objective: To determine the potential association between three age-related eye diseases and AD and dementia-related neuropathology.

Methods: We reviewed autopsy data from the prospective longitudinal Adult Changes in Thought (ACT) cohort. ICD-9 codes were used to identify diagnoses of diabetic retinopathy, glaucoma, and age-related macular degeneration. Multivariate regression models were used to determine odds ratios (OR) of neuropathology features associated with dementia, including Braak stage, Consortium to Establish a Registry for AD (CERAD score), Lewy bodies, hippocampal sclerosis, and microvascular brain injury, in addition to quantitative paired helical filament (PHF)-tau levels for people with and without each eye condition. We also evaluated interactions between eye conditions and dementia related neuropathologic findings were evaluated.

Results: 676 autopsies were included. Diabetic retinopathy was significantly associated with increased risk of deep cerebral microinfarcts (OR = 1.91 [95% confidence interval (CI) 1.11, 3.27], $p = 0.02$). No other significant association or interaction between eye diseases and neuropathology was found. When PHF-tau quantity was evaluated in 124 decedents, the OR for the association between PHF-tau in the occipital cortex and glaucoma was 1.36 (95% CI 0.91, 2.03, $p = 0.13$). No statistical correction was made for multiple comparisons.

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SUPPLEMENTARY MATERIAL

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Conclusion: Increased risk of deep cerebral microinfarcts was found in participants diagnosed with diabetic retinopathy. Eye diseases such as glaucoma may increase susceptibility to neurofibrillary tangles in the occipital cortex.

Keywords

Alzheimer's disease; diabetic retinopathy; glaucoma; macular degeneration; neuropathology

INTRODUCTION

As an extension of the central nervous system (CNS), the eye may offer opportunities to capture critical information regarding the health of the brain. Several ophthalmic conditions such as diabetic retinopathy (DR), glaucoma, and age-related macular degeneration (AMD) have been suggested to be associated with Alzheimer's disease (AD) and dementia, though studies are inconsistent in their findings [1–6]. Using the Adult Changes in Thought (ACT) study, a large, prospective, population-based cohort with research criteria of AD and dementia [7], we recently found that DR, glaucoma, and AMD were each significantly associated with development of clinical AD, while we found no association with cataract [8].

Comprehensive neuropathological evaluations are essential in understanding relationships between clinical phenotype, neurodegenerative disease, and associated co-morbidities revealed through AD epidemiological studies, but little is known about relationships between dementia-related neurodegeneration and eye diseases. Given significant associations between three neurodegenerative eye conditions and AD, we sought to determine the association between these conditions and common neurodegenerative conditions, including AD neuropathology, using data from the autopsy cohort from the ACT study.

In addition to standard diagnostic neuropathological criteria meeting or exceeding current guidelines for the entire cohort [9, 10], we also specifically considered highly quantitative, molecularly-specific data for paired helical filament (hyperphosphorylated) tau (PHF-tau) levels from occipital cortex including calcarine (primary visual) cortex. Retina is composed of retinal ganglion cells whose axons form the optic nerve and travel to the lateral geniculate nucleus and primary visual cortex in the occipital cortex. Thus, we hypothesized that abnormalities in the retina might alter susceptibility of occipital cortex to neurodegenerative processes associated with age-related dementia. We thus analyzed ACT autopsy data to test the hypothesis that eye diseases increase the risk of neurodegenerative disease neuropathology generally and specifically in the occipital cortex.

MATERIALS AND METHODS

Data came from the ACT study participants who had been prospectively evaluated, died between 11/22/1996 and 09/23/2016, and were autopsied at University of Washington (UW), Seattle, WA. ACT is a prospective, longitudinal, population-based cohort study that enrolls participants aged 65 and free of dementia from Kaiser Permanente Washington (KPW), a well-established comprehensive healthcare system in western Washington. Participants were

examined biennially either at home or clinic with a standard protocol, including administration of the Cognitive Abilities Screening Instrument (CASI) [11]. The CASI is a global cognitive test with scores that range from 0–100. Participants with scores ≥ 86 and any participants for whom the participant, staff, or family raised significant concerns were evaluated with a follow-up dementia detection evaluation. That evaluation included a comprehensive neuropsychological battery and a clinical examination along with medical records and imaging reviews. All of these data were reviewed at a consensus conference to diagnose and categorize dementia (probable versus possible AD versus other) using research quality criteria, described in detail elsewhere.[12, 13] The cohort is maintained at approximately 2,000 participants and approximately 30% consent for autopsy. This study was approved by the KPW and UW institutional review board.

Eye diagnosis

Eye diseases of interest were defined based on ICD-9 codes recorded at least once in participants' electronic medical records: DR (362.01, 363.02, 362.03, 362.04, 362.05, 362.06, 362.07), glaucoma (365.10, 365.11, 365.12, 365.13, 365.15), and AMD (362.50, 362.51, 362.2).

Neuropathologic features

Brain autopsy is performed on ACT participants with appropriate consent. At least 22 brain regions are sampled after appropriate fixation. Brain tissue is processed, and histologic sections are prepared with appropriate stains according to the latest guidelines [14]. Histologic sections are evaluated by a board certified neuropathologist and the following neuropathologic features graded as described previously [15, 16]: neurofibrillary tangle (NFT) distribution measured with Braak stage [17], neuritic plaque density quantified by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) level [18], Lewy bodies (presence or absence) [18, 19], hippocampal sclerosis (presence or absence), and cortical and subcortical (deep cerebral) microinfarcts evaluated as described in the Honolulu Asia Aging Study [20]. Cortical microinfarcts are defined from screening sections of the four lobes of cerebral cortex (middle frontal gyrus, superior/middle temporal gyri, inferior parietal lobule, and medial occipital lobe including calcarine fissure) while the deep cerebral microinfarcts are screening that include deep cerebral nuclei or the basal ganglia (caudate nucleus, putamen, striatum, globus pallidus at the level of the anterior commissure) and thalamus at the level of pulvinar.

Quantitative assessments of pathological tau

Quantitative data on tau from occipital cortex were available for a subset of the autopsy cohort. Selection for tau quantification was based on exposure to traumatic brain injury (TBI). There were 27 people selected on the basis of TBI exposure. There were two sets of comparison individuals selected for each exposed person. First, we selected people with no history of TBI who were matched on the basis of sex, age (within 2 years), and availability of frozen tissues (people with a short postmortem interval, defined as <8 h, had a rapid autopsy protocol with frozen brain tissues). Second, we selected people who were matched to TBI-exposed people in terms of age, sex, and frozen brain tissue availability, but who had low levels of neuropathology, defined as CERAD none or sparse, Braak stage 0–II, <2

microinfarcts, no Lewy bodies, and no hippocampal sclerosis. In this group, occipital cortex hyperphosphorylated tau was quantified using the histology and ELISA on a glass slide (Histelide) method. Details of the Histelide protocol have been described [21]. In brief, formalin-fixed, paraffin-embedded (FFPE) slides are incubated in PHF-tau primary antibody (AT8 clone, Thermo Fisher Scientific, Waltham, MA) followed by incubation in alkaline phosphatase conjugated secondary antibody. Next, slides are incubated in p-nitrophenol phosphate (pNPP) solution which reacts with the alkaline phosphatase to produce p-nitrophenol (pNP). Samples of this solution are extracted and measured for absorbance on a spectrophotometer. A 4-parameter logistic calibration curve is used to convert absorbance of pNP to concentration of pNP ($\mu\text{g}/\text{cm}^2$). Volume of pNPP is used to convert pNP concentration to pNP mass (μg). This measurement is normalized to slide tissue area resulting in a final unit of $\mu\text{g pNP}/\text{cm}^2$ tissue. Non-specific binding of the antibody is accounted for by exposing adjacent sections of tissue to appropriate IgG isotype control antibody. This non-specific background is subtracted from each sample. This allows a quantitative measurement of tissue area that reacts to PHF-tau antibodies.

Statistical analyses

We used logistic regression to determine odds ratios (OR) for each neuropathology outcome associated with each eye condition. We used generalized linear models with a log link to determine the distribution and OR of PHF-tau for people with and without each eye condition. We adjusted all models for age at death. Model fit was assessed by examining residuals and influence measures, and was found to be tenable in all models.

Because the autopsy cohort and the subset with Histelide are not representative of the general population, we used inverse probability weighting to extrapolate findings back to the study cohort [22–24]. We modeled probability of autopsy using a logistic regression model that included age at most recent study visit, sex, education, study entry cohort, and diagnosis of dementia. We used model results to determine each person's probability of being in the autopsy cohort, and used the inverse of this probability as the weight. Because the weights are derived from a model, it is important to incorporate uncertainty in the weights into the confidence intervals and tests of significance. We accomplished this using a bootstrapping procedure [23, 25, 26]. We used Stata (version 15.1; StataCorp) for all analyses.

Assessment of interactions

To explore the hypothesis that eye conditions might be associated with increased dementia risk through a possible alteration of cognitive resilience, we performed a series of additional analyses to investigate whether there were interactions between eye conditions and dementia risk associated with neuropathologic findings. The outcome for these models was dementia status at the time of death.

For these analyses we excluded 86 participants whose last ACT visit did not indicate dementia but had occurred more than 2.25 years before death, as we thought the dementia status at death would not be reliably known for this handful of individuals. The exposure measures for these analyses were DR, glaucoma, AMD. As in the primary analyses, each neuropathologic finding was dichotomized (e.g., Braak stage 0–IV versus Braak stage V–

VI). For each neuropathologic measure, we used logistic regression with main effects for eye diseases and the neuropathologic finding and the interaction terms between them, controlling for age at death.

RESULTS

Participant characteristics

Autopsy data were available for 676 people from the ACT study. The mean age at death was 88.1 years (SD 6.7 years) and 43% were male. The average interval between last clinical visit and death was 2.5 years (SD 2.4 years) and the median clinical follow-up of participants was 15.8 years. 373 (55%) participants had any of three eye diagnoses (DR, glaucoma, AMD); 61 (9%) had DR, 246 (22%) had glaucoma, 273 (40%) had AMD, and 97 had more than 2 eye diagnoses (Table 1).

Associations between eye diseases during life and traditional neuropathology features at autopsy

The distributions of neuropathologic features in participants are shown in Table 2. No associations were found between eye diagnoses and Braak stage, CERAD level, presence of Lewy bodies, or presence of hippocampal sclerosis (Supplementary Table 1).

There were 347 people with microinfarcts. Of these, 246 had cortical microinfarcts, and 221 had deep microinfarcts; 120 had both cortical and deep microinfarcts, 126 had only cortical infarcts, and 101 had only deep microinfarcts. DR was associated with a greater risk for deep microinfarcts (OR = 1.91, 95% confidence interval 1.11, 3.27, $p = 0.02$), but there was no association with cortical microinfarcts. Weighted back to the full cohort, the OR for deep microinfarcts was 1.66 (0.85, 3.12). We also analyzed whether a higher risk for deep microinfarcts was associated with systemic diabetes with or without DR. The OR for deep microinfarcts for diabetes without DR was 1.12 (0.63, 2.03) $p = 0.715$ but for diabetes with DR was 1.92 (1.12, 3.32) $p = 0.018$. No microinfarct associations were found for glaucoma or AMD (Table 3).

No significant interactions for dementia risk were found between traditional neuropathologic findings with any of the three eye conditions.

Associations between eye diseases during life and tau pathology in occipital cortex at autopsy

Out of our cohort, 115 people had Braak V and 109 had Braak VI. We hypothesized that among people with tangles spread to cortex (i.e., Braak stage at least V), spread to occipital including primary visual cortex in particular (i.e., Braak VI) could be related to eye diseases. However, having any of three eye conditions (DR, glaucoma, or AMD) was not significantly associated with higher risk of Braak VI, with OR 1.13 (0.65, 1.97; $p = 0.66$). ORs for Braak VI with DR, glaucoma, and AMD were 1.43 (0.44, 4.64; $p = 0.55$), 1.03 (0.55, 1.94, $p = 0.93$), and 0.92 (0.53, 1.60; $p = 0.78$), respectively.

In a small subset of participants ($n = 124$), tau pathology from occipital cortex was quantified as a continuous variable using Histelide. In this population, 63 (51%) had at least

one eye disease (13 had DR, 23 had glaucoma, and 47 had AMD). Glaucoma was associated with 36% higher PHF-tau levels in occipital cortex but this was not statistically significant ($p = 0.13$). Weighted back to the full cohort, the risk was 1.30 (0.81, 2.01).

DISCUSSION

Diabetic retinopathy was significantly associated with increased risk of deep microinfarcts. Using a highly quantitative method to measure PHF-tau in the occipital cortex, higher PHF-tau was associated with glaucoma although it did not reach statistical significance.

There are multiple lines of evidence that support a relationship between age-related neurodegeneration and eye diseases, principally concerning the microvasculature of the retina and the brain [27]. Embryologically, the retina develops from the diencephalon, and there are coordinated patterns of vascularization during development [28] resulting in similarities between the macrovascular and microvascular blood supply to the brain and the retina [29, 30]. Clinically, larger retinal venular diameters have been associated with increased risk of vascular dementia [31] and progression of cerebral small vessel disease [32], and narrower arteriolar and wider venular retinal diameters are associated with reduced white matter volume [33]. Therefore, conditions that affect retinal microvasculature are thought to act similarly on brain microvasculature and downstream neurological injury. In addition to similarities in vasculature, the retina is directly connected to the brain through retina ganglion cell processes that comprise the optic nerves and is considered an extension of the central nervous system. Thus, structural and pathophysiological processes that affect the retina may affect change in the brain either by anterograde or retrograde degenerative mechanisms. In support of this possibility, many studies have shown that decreased thickness of retinal nerve fiber layer and ganglion cell layer as assessed using advanced ophthalmic imaging such as optical coherence tomography may be associated with cognitive decline or clinical AD [34–37]. However, to our knowledge, no studies have shown direct correlations between eye diseases and neuropathological features found at autopsy.

Despite the small sample size with DR in our cohort, we found a nearly 2-fold higher risk of deep cerebral microinfarcts associated with DR. It is interesting that we saw significant associations between deep microinfarcts and DR but not with systemic diabetes alone, indicating that DR likely represents either a more advanced state of systemic diabetes and/or specific microvascular injury in the retina that correlates to that of brain. Although future studies, including experimental models, are necessary to definitively determine common mechanisms, the relationships between DR and microinfarcts with small vessel disease and microscopic injury suggest a common mechanism at the capillary or arteriolar level [38]. Cerebral microinfarcts are thought to represent diffuse abnormalities of small vessels and can be considered within the spectrum of small vessel disease [39]. Similarly, DR is a disease of retinal microvasculature and a marker of blood retinal barrier loss. The loss of endothelial pericytes is believed to be the initiating pathology of DR [40], and similar loss of endothelial integrity of brain microvasculature may take place in patients with DR. Future studies are indicated to test this hypothesis. The relationship of DR to deep cerebral, but not cortical, microinfarcts is interesting and may be related to different source vasculature and

potentially related to increased propensity for lacunar infarcts (small macroinfarcts) in deep cerebral nuclei.

Several potential confounders must be considered in evaluating associations between DR and deep cerebral microinfarcts. Both conditions are associated with systemic vascular risk factors such as hypertension, cardiovascular disease (e.g., myocardial infarction, angioplasty), and cerebrovascular disease (e.g., stroke) [41–43]. We have controlled for these potential confounders in our models, but residual confounding may still exist. In addition, other variables such as fasting blood glucose, HbA1C, BMI, cholesterol, triglycerides, atherosclerosis and arteriolosclerosis that have been associated with diabetic retinopathy or cerebral microinfarcts may confound our findings [43, 44]. Thus future studies that incorporate assessment of these clinical variables would be important in enlightening the shared mechanism between DR and deep microinfarcts.

There are potential clinical implications to the strong correlation between DR and deep cerebral microinfarcts. Given that DR can be detected *in vivo* non-invasively, dilated fundoscopic examination could potentially be used as a screening tool to identify people more likely to have microvascular brain injury [45]. However, cortical microinfarcts, rather than subcortical microinfarcts, have been specifically associated with dementia risk; thus, a study with larger sample size to confirm our results, and prospective cohort trials to further assess this possibility, may be warranted [16, 39]. In addition, further studies that incorporate severity or subtypes of DR in relation to the location and quality of cerebral microinfarcts may be informative. Finally, this and related findings strengthen the association between diabetes and dementia and provide further foundation for experimental approaches to understand mechanisms and develop therapies.

We also sought to examine potential associations between eye conditions and NFT distribution and A β neuritic plaque density, key neuropathological features of AD. The occipital cortex is one of the last areas involved by NFT. Because the ocular system connects to the brain at the occipital cortex through a single synaptic junction in the lateral geniculate nuclei, we hypothesized that NFT pathology would be more common in participants with eye conditions than in those without, resulting in higher risk of Braak VI than Braak V. However, it is also possible that people may be susceptible for NFT pathology in the retina and the occipital cortex independently from each other. Having any of three eye conditions (DR, glaucoma, or AMD) was not significantly associated with higher risk of Braak VI, with RR 1.07 ($p = 0.74$).

Even though we did not find any association between eye conditions and neuropathology end-points as categorical variables, we found an increased trend for pathological tau in the occipital cortex among participants who had glaucoma when PHF-tau was quantified using Histelide. This quantitative assessment evaluates all pathological tau in the parenchyma, including that in NFTs, neuritic plaques, affected neurites, and even glial tau. Because Histelide provides a continuous, highly quantitative variable, it may be more sensitive to detect differences in tau pathology, or occipital tau may be present in large part in compartments other than NFT, which are not evaluated as part of classical Braak staging. This finding suggests that retina ganglion cells may influence cerebral cortical (occipital)

PHF-tau deposition. Retinal ganglion cells are terminally differentiated CNS neurons with their axons primarily affected. Even in mild glaucoma without any visual field defect, approximately 50% of ganglion cells are already lost [46, 47]. Thus, any diagnosis of glaucoma will be associated with a significantly decreased afferent input to lateral geniculate nucleus and eventually occipital cortex. The trend for increased PHF-tau in the occipital cortex among participants with glaucoma may indicate that ganglion cell activity-dependent function may serve a protective role against tau pathology in the occipital cortex.

Several limitations exist in our study. First, the status of eye diseases was based on ICD-9 codes and we did not have any clinical data regarding the severity of each eye disease. It is possible that the association strength we found with microinfarcts and possibly with tangles may be different if severity data of each condition were incorporated in the analyses. In particular, given that we only found significant associations between deep microinfarcts and diabetes with DR and not diabetes without DR, the DR severity data could be useful to distinguish whether the risks for DR represent a more severe state of systemic diabetes and/or an additional pathology linked to that of the brain. Second, our sample size was limited in the quantitative analysis of PHF-tau. The fact that we found a trend for increased PHF-tau but not NFT suggests that our analyses of neuropathology with categorical variables may not be sufficiently sensitive. Future studies that allow quantitative analyses of traditional neuropathology features will be important. Third, the participants who consent for autopsy are not representative of general population. Although we accounted for this difference with inverse probability weighting in our analyses, our findings may not be generalizable in other populations. Fourth, our study cannot determine whether eye disease is a cause, an effect, or a coincidental pathology relative to cerebral findings assessed on autopsy. However, our results connecting the eye and neuropathology are worthy of further investigations. Lastly, we looked for interactions using appropriate models, despite the smaller numbers that suggested such an interaction would need to be very strong for us to detect it. We did not find any significant interactions between eye conditions and traditional neuropathology endpoints. However, a larger sample size may show different findings. Our study design was exploratory, and we did not correct for multiple comparisons. Thus, our study will need to be replicated in another cohort.

In summary, increased risk of deep cerebral microinfarcts was found in participants diagnosed with DR. Eye diseases may increase susceptibility to pathological tau deposition in the occipital cortex. Further studies to explore the specific aspects of DR that may explain associations with deep microinfarcts and the potential associations between glaucoma and tau pathologies are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Study participant characteristics stratified by eye diagnoses

	No eye diagnoses (<i>n</i> = 303)	Any eye diagnoses (<i>n</i> = 373)	DR (<i>n</i> = 61)	Glaucoma (<i>n</i> = 146)	AMD (<i>n</i> = 273)
Mean age at death (SD)	86.3 (6.9)	89.7 (6.1)	86.2 (5.3)	89.5 (6.2)	90.4 (6.1)
Male	144 (48%)	145 (39%)	31 (51%)	59 (40%)	100 (37%)
Caucasian	279 (92%)	363 (97%)	58 (95%)	141 (97%)	269 (99%)
Post HS education	208 (69%)	253 (68%)	40 (66%)	102 (70%)	185 (68%)
APOE ε4	89 (31%)	93 (26%)	17 (29%)	38 (27%)	56 (21%)
Hypertension	172 (57%)	235 (63%)	48 (79%)	92 (63%)	172 (63%)
Diabetes	36 (12%)	75 (20%)	55 (90%)	29 (20%)	37 (14%)
Cardiovascular disease	79 (26%)	129 (35%)	27 (44%)	48 (33%)	90 (33%)
Cerebrovascular disease	87 (29%)	116 (31%)	26 (43%)	44 (30%)	81 (30%)
Current Smoker	13 (4%)	8 (2%)	1 (2%)	3 (2%)	6 (2%)

* People could develop more than one ophthalmic disease so the last 3 columns are not mutually exclusive groups. DR, diabetic retinopathy; AMD, age-related macular degeneration; HS, high school; Cardiovascular disease defined as any history of myocardial infarction, angina, coronary artery bypass grafting, or angioplasty; Cerebrovascular disease defined as any history of stroke, transient ischemic attack, or carotid endarterectomy.

Table 2

Neuropathology features present in study participants stratified by eye diagnoses

	No eye diagnoses	DR	Glaucoma	AMD
Braak stage				
Braak Stage 0–II	116 (9)	19 (31%)	38 (26%)	85 (31%)
Braak Stage III–IV	93 (31%)	29 (48%)	56 (38%)	88 (32%)
Braak Stage V	47 (16%)	5 (8%)	27 (18%)	55 (20%)
Braak Stage VI	45 (15%)	8 (13%)	25 (17%)	45 (16%)
CERAD				
Low level (0–1)	153 (51%)	30 (49%)	70 (48%)	123 (45%)
High level (2–3)	150 (50%)	31 (51%)	76 (52%)	150 (55%)
Lewy Body				
Present	51 (17%)	6 (10%)	23 (16%)	220 (83%)
Absent	243 (83%)	54 (90%)	119 (84%)	46 (17%)
Hippocampal Sclerosis				
Present	27 (9%)	3 (5%)	21 (15%)	38 (14%)
Absent	267 (91%)	55 (95%)	123 (85%)	230 (86%)
Microinfarcts				
Cortical microinfarcts	105 (35%)	21 (34%)	56 (39%)	107 (39%)
Deep microinfarcts	86 (28%)	27 (44%)	47 (33%)	100 (37%)

Table 3

Odds Ratios (95% confidence intervals (CI)) between eye diseases during life and microinfarcts at autopsy, controlling for age at death

Condition	Cortical microinfarcts OR (95% CI), <i>p</i>	Deep microinfarcts OR (95% CI), <i>p</i>	Any microinfarcts OR (95% CI), <i>p</i>
DR	1.01 (0.58, 1.77), <i>p</i> = 0.97	1.91 (1.11, 3.27), <i>p</i> = 0.02	1.27 (0.74, 2.17), <i>p</i> = 0.38
Glaucoma	1.05 (0.71, 1.54), <i>p</i> = 0.81	0.92 (0.62, 1.37), <i>p</i> = 0.69	1.08 (0.74, 1.57), <i>p</i> = 0.69
AMD	1.02 (0.73, 1.43), <i>p</i> = 0.90	1.17 (0.84, 1.65), <i>p</i> = 0.35	1.19 (0.86, 1.65), <i>p</i> = 0.30

OR, odds ratio; DR, diabetic retinopathy; AMD, age-related macular degeneration.

Table 4

PHF-tau in occipital cortex at autopsy and between eye diseases during life, odds ratios (95% confidence intervals (CI)), $n = 124$

Condition	Median (Interquartile range) of PHF-tau (n)		OR (95% CI), p
	Without condition	With condition	
DR	0.14 (0.04, 0.26) ($n = 111$)	0.09 (0.00, 0.19) ($n = 13$)	0.97 (0.48, 1.96), $p = 0.94$
Glaucoma	0.10 (0.03, 0.23) ($n = 101$)	0.18 (0.09, 0.35) ($n = 23$)	1.36 (0.91, 2.03), $p = 0.13$
AMD	0.13 (0.03, 0.25) ($n = 77$)	0.14 (0.04, 0.27) ($n = 47$)	1.05 (0.71, 1.55), $p = 0.80$

OR, Odds ratio; DR, diabetic retinopathy; AMD, age-related macular degeneration.