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## ORIGINAL ARTICLE

# EVALUATION OF COGNITIVE IMPAIRMENTS IN GLAUCOMA SUBTYPES: PRIMARY OPEN-ANGLE GLAUCOMA, PSEUDOEXFOLIATION SYNDROME, AND PSEUDOEXFOLIATION GLAUCOMA

## ABSTRACT

**Introduction:** Pseudoexfoliation syndrome is an age-related condition characterized by abnormal fibrillar material accumulation in the ocular and systemic tissues. Several studies have suggested that pseudoexfoliation syndrome is associated with neurodegenerative processes via different mechanisms. In our study, cognitive function was evaluated using the Mini-Mental State Examination in patients with pseudoexfoliation syndrome, pseudoexfoliation glaucoma, and primary open-angle glaucoma and compared with healthy controls.

**Materials and Method:** In this prospective study, 43 patients aged  $\geq 60$  years were diagnosed with pseudoexfoliation syndrome (Group I), 40 with pseudoexfoliation glaucoma (Group II), 43 with primary open-angle glaucoma (Group III), and 72 healthy individuals who served as controls (Group IV). The Mini-Mental State Examination was administered in a quiet room by the same neurologist who was blinded to the participants' diagnoses.

**Results:** A statistically significant difference was observed among the groups in Mini-Mental State Examination scores ( $p=0.001$ ). Pairwise comparisons adjusted using the Bonferroni correction revealed significant differences between Groups I and IV, Groups II and III, and Groups II and IV ( $p=0.036$ ;  $p=0.036$ ;  $p=0.0012$ , respectively). In patients with pseudoexfoliation syndrome, Mini-Mental State Examination scores inversely correlated with age ( $p=0.003$ ,  $r=-0.323$ ); however, this association was not observed in the other groups ( $p=0.09$ ).

**Conclusion:** Mini-Mental State Examination scores were significantly lower in patients with pseudoexfoliation syndrome and pseudoexfoliation glaucoma than in the control group and patients with primary open-angle glaucoma. Additionally, Mini-Mental State Examination performance inversely correlated with age in the pseudoexfoliation group. These findings suggest that pseudoexfoliation may not be confined to ocular pathology alone but may also be associated with systemic cognitive impairment.

**Keywords:** Exfoliation Syndromes; Glaucoma, Open-Angle; Cognition; Mental Status and Dementia Tests; Alzheimer Disease; Aged.

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## INTRODUCTION

Pseudoexfoliation syndrome (PXS) is the accumulation of abnormal extracellular fibrillar deposits in age-related intraocular and extraocular systemic tissues (1,2). The accumulation of these abnormal fibrils in the trabecular meshwork obstructs aqueous outflow and increases intraocular pressure (IOP). PXS is the most common identifiable cause of secondary glaucoma, and when accompanied by elevated IOP and glaucomatous optic neuropathy, it is termed pseudoexfoliative glaucoma (PXG). PXG follows a more aggressive clinical course than primary open-angle glaucoma (POAG) and exhibits a poorer response to topical therapy. In addition to glaucoma, the presence of pseudoexfoliated material contributes to cataract formation, lens subluxation, and increased intraoperative difficulty (3).

Abnormal fibrillar deposits have also been identified in various systemic organs, including vascular structures, the heart, lungs, kidneys, liver, skin, and meninges (3). Consequently, PXS has been associated with multiple systemic conditions such as hypertension, stroke, aneurysm formation, and renal artery stenosis. It has been reported that the abnormal elastic microfibrillar aggregates characteristic of PXS share similarities with the amyloid accumulation observed in Alzheimer's disease (AD) (4,5). Moreover, amyloid and alpha-1 antichymotrypsin, enzymes involved in the regulation of amyloid formation, have been detected in pseudoexfoliation materials (4). The aim of the present study was to compare the cognitive functions of patients diagnosed with PXS, PXG, and POAG using the Mini-Mental State Examination (MMSE).

## MATERIALS AND METHOD

This prospective study evaluated patients who visited the Ophthalmology Outpatient Clinic at Akdeniz University between September 2013 and June 2014. Patients aged 60 years or older, whose native language was Turkish, who had received at

least eight years of formal education, and who did not report hearing impairment that could interfere with their cooperation in the MMSE were included. Patients with chronic neurological disorders (such as epilepsy, stroke, Parkinson's Disease or dementia); mental retardation; chronic heart or kidney failure; insulin-dependent diabetes mellitus; age-related macular degeneration; retinal vascular diseases; a history of ophthalmic surgery; ocular trauma; uveitis; or any ocular condition that could affect the evaluation of the iris, lens, or optic disc were excluded. Given the reported association between pseudoexfoliation syndrome and systemic or ocular vascular conditions, patients with major vascular comorbidities that could independently influence cognitive performance or ophthalmic findings were excluded. The study was not designed to establish a diagnosis of dementia; therefore, neuroimaging studies such as brain MRI were not routinely performed. Individuals with corrected visual acuity below 20/40, except for those with cataracts, were also excluded. The control group consisted of relatives of patients with no chronic systemic illnesses.

All participants underwent a comprehensive ophthalmological examination that included detailed ocular history, best-corrected visual acuity, slit-lamp examination after pupillary dilation, Goldmann applanation tonometry, gonioscopy with Goldmann's three-mirror lens, visual field testing, and fundus examination. Pseudoexfoliative material was assessed after dilation, and the presence of fibrillar deposits in the anterior segment, whether unilateral or bilateral was defined as PXS. PXG was diagnosed based on the presence of pseudoexfoliative material on the anterior segment, together with glaucomatous optic neuropathy characterized by an increased cup-to-disc ratio and/or neuroretinal rim thinning, and corresponding visual field defects, with or without elevated intraocular pressure. POAG was diagnosed based on an open anterior chamber angle on gonioscopy, the presence of glaucomatous optic neuropathy, and corresponding reproducible visual field defects.

The study was not designed to establish a diagnosis of dementia; therefore, neuroimaging studies such as brain MRI were not routinely performed. Cognitive assessment was conducted using the MMSE, a widely used screening tool for global cognitive status. The MMSE evaluates orientation, registration, attention and calculation, recall, language, and visuospatial abilities, and requires approximately 5–10 minutes to administer. The MMSE, whose Turkish validity and reliability have been established, was administered in a quiet room by a neurologist blinded to the patient and control groups (6). In the present study, MMSE scores were classified as  $\leq 19$  indicating moderate to severe cognitive impairment, 20–25 indicating mild cognitive impairment, and  $\geq 26$  indicating normal cognitive performance. In patients who underwent cataract surgery, the MMSE was administered only after postoperative improvement in visual acuity. Although hemispheric dominance was not a primary focus of the study, recording dominant hand aimed to reduce potential confounding effects on cognitive screening results.

The study was approved by the Ethics Committee of the Akdeniz University, Faculty of Medicine (reference number: 15.05.2013/93), and written informed consent was obtained from all participants.

### Statistical Analysis:

Statistical analyses were performed using SPSS software (version 16.0; SPSS Inc., Chicago, IL, USA).

Data were presented as mean  $\pm$  standard deviation, while categorical variables were expressed as numbers and percentages. The chi-square test was used to compare categorical variables, and the Mann–Whitney U test was used to compare continuous variables. For multiple group comparisons, the Kruskal–Wallis test with Bonferroni correction was used. Quantitative relationships between variables that did not follow a normal distribution were assessed using Spearman’s correlation coefficient, whereas Pearson correlation test was used for variables that showed a normal distribution.

### RESULTS

A total of 198 patients who met the inclusion criteria were enrolled in this study. Of these, 106 (53.5%) were female and 92 (46.5%) were male. Group I (PXS) consisted of 43 patients; Group II (PXG), 40 patients; Group III (POAG), 43 patients; and Group IV (control group), 72 patients. The mean age of all participants was  $70.9 \pm 5.9$  years. No statistically significant differences were observed between the groups in terms of age or sex ( $P > 0.05$ ). A total of 191 patients were right-handed, and seven were left-handed. The demographic characteristics of the study groups are shown in Table 1. Dominant hand was recorded to account for potential effects of hemispheric dominance on cognitive performance.

The mean MMSE scores in the groups were  $25.8 \pm 3.4$ ,  $25.5 \pm 3$ ,  $27 \pm 2.4$ , and  $27.4 \pm 2.1$ , respectively.

**Table 1.** Demographic characteristics of the study groups

	Group I (PXS)	Group II (PXG)	Group III (POAG)	Group IV (Control)
Number of patients (n)	43	40	43	72
Female/Male (n)	19/24	21/19	40/32	26/17
Age	$72.3 \pm 6.9$	$71.8 \pm 6.7$	$70.1 \pm 5.6$	$70.5 \pm 4.8$
Dominant hand (left/right)	2/41	1/39	3/40	1/71
MMSE	$25.8 \pm 3.4$	$25.5 \pm 3$	$27 \pm 2.4$	$27.4 \pm 2.1$

MMSE: Mini-Mental State Examination, PXS: Pseudoexfoliation syndrome, PXG: Pseudoexfoliative glaucoma, POAG: Primary open-angle glaucoma



**Table 2.** Distribution of MMSE scores across subgroups

MMSE	Group I (PXS)	Group II (PXG)	Group III (POAG)	Group IV (Control)	Total (n=198)
≤ 19	4	2	1	0	7
20-25	13	15	7	8	44
≥26	26	23	35	63	147

MMSE: Mini-Mental State Examination, PXS: Pseudoexfoliation syndrome, PXG: Pseudoexfoliative glaucoma, POAG: Primary open-angle glaucoma

MMSE scores differed significantly between the groups ( $p=0.001$ ). In pairwise comparisons using Bonferroni correction, statistically significant differences were found between Groups I and IV, Groups II and III, and Groups II and IV ( $p=0.036$ ,  $p=0.036$ , and  $p=0.0012$ , respectively), whereas no significant differences were detected in the remaining comparisons. A negative correlation between MMSE scores and age was observed in patients with PXS ( $p=0.003$ ;  $r=-0.323$ ), but no such correlation was found in patients without PXS ( $p=0.09$ ). The mean MMSE score was  $26.5 \pm 3$  in women and  $26.7 \pm 2.5$  in men, with no statistically significant difference between sexes ( $p=0.74$ ).

A total of 51 patients (25.3%) had an MMSE score  $< 26/30$ , and the presence of PXS was significantly higher in this group ( $p=0.000025$ ). Of these, 17 (34%) were in Group I, 17 (34%) in Group II, 8 (16%) in Group III, and 8 (16%) in Group IV. The distribution of MMSE scores across the subgroups is presented in Table 2. There was no significant difference in whether PXS was bilateral or unilateral ( $p=0.52$ ). PXS was present in both eyes of 48 patients, the left eye of 25 patients, and the right eye of 10 patients.

## DISCUSSION

In this study, the cognitive function of patients diagnosed with PXS, PXG, and POAG was evaluated using the MMSE. MMSE total scores differed significantly between groups. This difference was most apparent in the PXS group, which had lower scores than the control group,

and in the PXG group, which had lower scores than those of the POAG and control groups. No significant differences were observed in the remaining pairwise comparisons. Additionally, PXS was significantly more common among the 51 patients with an MMSE score  $< 26/30$  ( $p=0.000025$ ). The negative correlation between MMSE scores and age in patients with PXS further supports the notion that PXS may have an age-related impact on cognitive function. Cognitive findings were based on screening assessment, and no participant was started on treatment for cognitive impairment during the study period. Although dominant hand was recorded to account for potential effects of hemispheric dominance on cognitive performance, the majority of both patients and controls were right-handed. Therefore, hemispheric dominance is unlikely to have significantly influenced the MMSE results in the present study.

AD is the most common progressive neurodegenerative disorder, characterized by cognitive decline and subsequent impairment of activities of daily living. AD and glaucoma are age-related disorders that exhibit neurodegenerative features and share partially overlapping biological mechanisms. In both conditions, factors such as neuroinflammation, elevated tumor necrosis factor-alpha (TNF- $\alpha$ ) levels, and upregulation of complement component C1q contribute to pathogenesis (7). It has been demonstrated that A $\beta$  1–42 levels decrease in the cerebrospinal fluid of patients with AD and in the vitreous fluid of patients

with glaucoma, while tau protein levels increase (4). In an experimental glaucoma model, chronic ocular hypertension was shown to enhance A $\beta$  production through abnormal processing of amyloid precursor protein (APP) and caspase activation (8). This creates a vicious cycle involving APP accumulation, caspase activation, and increased A $\beta$  synthesis, ultimately leading to retinal ganglion cell loss and neuronal degeneration. This mechanism provides an important model that may explain the progressive nature of glaucoma and its potential pathogenic link to AD (8). Overall, current evidence suggests that pseudoexfoliation and glaucoma shares several biochemical and pathological features with neurodegenerative processes, including amyloid accumulation, oxidative stress, and neuroinflammation.

A comprehensive meta-analysis by Xu et al. reported that the risk of developing AD was significantly higher in patients with glaucoma than in those without glaucoma (9). However, findings across studies have not been entirely consistent. A large population-based study (Beijing Eye Study) reported no significant association between open-angle glaucoma or pseudoexfoliation and MMSE scores, highlighting the complexity and potential heterogeneity of the relationship between ocular diseases and cognitive function(10).

In a community-based 30-year longitudinal cohort study, pseudoexfoliation was not identified as a predictor of AD, and no significant association was found between POAG and AD (11). However, the methodological limitations of this study may limit the strength of its conclusions. For example, dementia diagnoses were based solely on clinical evaluations, and cases of AD, mixed dementia, and undiagnosed dementia were grouped into a single category. This approach likely increases diagnostic heterogeneity, making it difficult to clarify the potentially specific relationship between PXS and AD. Furthermore, the small number of reported Alzheimer's disease cases may have contributed

to the conclusion that pseudoexfoliation is not a precursor to AD.

In a cross-sectional study, 67 patients diagnosed with PXS were compared with 67 age- and education-matched controls. The prevalence of AD was 67.2% in the PXS group and 26.9% in the control group, a statistically significant difference (12).

A total of 48 patients with PXS, subdivided into those with and without glaucoma, were compared with 48 age- and sex-matched healthy controls retrospectively. Global cortical, posterior parietal, and medial temporal lobe atrophy were evaluated using visual rating scales on brain MRI scans. Global cortical and parietal atrophy scores were significantly higher in the PXS group, whereas medial temporal atrophy was more prevalent, although not statistically significant. Additionally, although not statistically significant, an inverse correlation was observed between PXG severity and the MMSE score (13). In Alzheimer's disease, MMSE scores typically decline to below 26 in mild stages and further decrease with disease progression. In the our study, mean MMSE scores in all groups largely remained within the non-demented range, supporting the interpretation that the observed differences likely represent subtle or subclinical cognitive changes rather than clinically overt dementia.

### **Limitations**

The primary limitation of this cross-sectional study is that cognitive function was assessed using a single screening tool (MMSE), without comprehensive neuropsychological evaluation. Therefore, the findings should be interpreted with caution and considered hypothesis-generating rather than definitive, given the observational design. Another limitation is that the data were collected between 2013 and 2014; however, the clinical association between pseudoexfoliation-related conditions and cognitive function remains relevant. In addition, the relatively small sample size limits the generalizability of the results.



Furthermore, detailed quantitative ophthalmic parameters reflecting glaucomatous disease severity, such as standardized visual field indices or structural measurements, were not available. As a result, the relationship between the extent of glaucomatous damage and cognitive performance could not be formally analyzed, as the study focused on cognitive screening in patients with established ophthalmic diagnoses rather than on disease severity.

## CONCLUSION

MMSE scores were significantly lower in patients with PXS and PXG. MMSE scores also showed a significant negative correlation with age in patients with PXS and PXG, whereas no such relationship was observed in the control group. Although the present study could not directly determine the relationship between PXS and AD, it demonstrated that cognitive function is reduced in individuals diagnosed with PXS and PXG. This finding is consistent with the literature, suggesting that PXS is not merely an ocular disorder but a systemic microfibriolopathy that may also affect central nervous system involvement. Future longitudinal studies with larger sample sizes, comprehensive neurocognitive assessments, and neurologist-confirmed dementia diagnoses are warranted to better clarify the relationship between pseudoexfoliation and cognitive impairment.

**Conflict of Interest Statement:** The authors declare that they have no conflict of interest regarding this study.

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