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The relationship between dry eye disease and anticholinergic burden

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PURPOSE: Anticholinergic drugs are widely prescribed for many medical conditions. However, data on the association of anticholinergic burden with dry eye disease (DED) are limited. In this study, we aimed to examine the relationship between anticholinergic burden and DED.

METHODS: In this retrospective cohort study, we evaluated a total of 120 participants who underwent ophthalmological examination between February 2021 and February 2022. The drugs used by the patients in the last 2 months were recorded from the institute's electronic data system. Anticholinergic burden was assessed using the Anticholinergic Cognitive Burden (ACB) scale.

RESULTS: The mean age of those patients was 59.0 ± 11.6 years and more than half ($n = 33$, 64.7%) were women. Patients with DED had significantly higher Charlson comorbidity index scores ($p = 0.01$), lower Schirmer test values ($p = 0.01$), higher Ocular Surface Disease Index (OSDI) scores ($p = 0.01$), and higher anticholinergic burden ($p = 0.01$). There was a statistically significant positive correlation between ACB and OSDI scores ($r = 0.22$, $p = 0.02$) and a negative correlation between ACB scores and Schirmer test values ($r = -0.46$, $p = 0.01$). After adjusting for potential confounding factors (age, gender, and comorbidities), each 1-point increase in anticholinergic burden was found to result in a 2.97-fold increase in the risk of DED (OR: 2.97, 95% confidence interval: 1.22–7.24, $p = 0.02$).

CONCLUSION: Anticholinergic burden appears to be associated with DED. Therefore, greater caution in prescribing anticholinergic drugs for adult patients may be important in reducing the rates of many adverse outcomes.

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INTRODUCTION

Dry eye disease (DED) is a common, complex, multifactorial condition that causes ocular discomfort, often with symptoms such as dryness, burning, and stinging [1]. The prevalence of DED ranges from 5% to 50% and it significantly affects patients' quality of life [2–4]. The aetiology of DED has yet to be clearly elucidated, but it is believed to be multifactorial [5, 6]. There are many changeable and unchangeable risk factors such as advanced age, female gender, autoimmune diseases, environmental exposures, and drug use [7]. A series of topical and systemic drugs, including antidepressants, antihypertensives, anti-glaucoma drugs, and anticholinergics, have been associated with the signs and symptoms of DED [8–10].

As is known, many drugs exert anticholinergic activities, meaning that they block the binding of acetylcholine, a neurotransmitter, to the muscarinic receptor [11, 12]. In such cases, the occurrence of anticholinergic side effects are inevitable [13]. Central effects such as cognitive impairment, dizziness, sedation, confusion, or delirium, as well as peripheral effects such as dry mouth, dry eyes, constipation, urinary retention, and tachycardia, start being observed [14]. The notion of "anticholinergic burden" is related to the cumulative effect of one or more drugs that have anticholinergic activity [15, 16]. This cumulative effect is a strong indicator of cognitive and physical impairment, particularly in the elderly population [17]. It is also associated with adverse consequences such as falls, impairment in functionality, and higher rates of hospital admission and mortality [18–20].

Anticholinergic load scales are scales facilitating the work of physicians, used in clinical practice to predict anticholinergic side effects in humans [21]. There are many different scales used for this purpose, but among them, the Anticholinergic Cognitive Burden (ACB) scale has the highest validity and reliability according to recent studies [16, 22].

Ascertaining the full roles of systemic and topical drugs, which are among the aetiologies of dry eye, is of great importance because this can provide clues about the multifactorial pathophysiology of dry eye and can help alleviate the clinical condition for patients by allowing the replacement of those drugs [23]. In this study, we aimed to investigate the relationship between anticholinergic burden and DED. We secondarily aimed to evaluate the relationship between anticholinergic burden and Schirmer test and Ocular Surface Disease Index (OSDI) scores.

MATERIALS AND METHODS

Study design, setting, and sample

This retrospective cohort study was begun with a total of 506 patients who applied to the Kırşehir Ahi Evran Training and Research Hospital

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Ophthalmology Outpatient Clinic between February 2021 and February 2022. Patients with an eye disease that had previously been diagnosed by an ophthalmologist, those younger than 18 years of age, those with severe organ failure (hepatic or renal), those with a history of active infection, and those with functional cognitive impairment were excluded from the study. A total of 120 people were subsequently enrolled in the study. Due to the retrospective nature of the study design, the need for informed consent was waived. Before starting the study, approval was obtained by applying to the Medical, Surgical, and Pharmaceutical Research Ethics Committee of Kırşehir Ahi Evran Training and Research Hospital (2022-02/13).

Diagnosis of dry eye disease

Routine ophthalmological examinations of the participants were conducted by the same person on the date of their presentation to the clinic (index data). Amounts of reflex tears were evaluated by performing the Schirmer I test without local anaesthesia. Values below 5 mm were considered as evidence of severe DED [24].

Patients were subjected to the OSDI test, which determines the severity of DED. This test, consisting of twelve questions, was intended to identify the complaints of patients about dry eyes over the previous two weeks. Questions addressed ocular symptoms, environmental triggers, and vision-related functions. The severity of the patients' exposure was scored on a scale from 0 ("never") to 4 ("always") and the OSDI score was calculated as follows: OSDI = Total score of all questions answered × 100/Total number of questions answered × 4. The maximum possible OSDI score was 100, while the minimum possible value was 0 [25].

Assessment of anticholinergic burden

When evaluating the anticholinergic burden for each patient, dates of admission to the outpatient clinic were considered for index data. Drugs started or continuing to be used in the last 2 months prior to that date were recorded based on the patients' statements. These data were then verified by reviewing the national electronic database records [26]. Anticholinergic burden was calculated by using the ACB scale [27]. On this scale, drugs are classified based on their anticholinergic properties on a scale of 0 to 3 [28]. An ACB score of 0 represents the absence of anticholinergic effects. An ACB score of 1 represents possible anticholinergic effects, while ACB scores of 2 and 3 represent definite anticholinergic effects [27, 28]. For each patient, total anticholinergic burden (i.e., total ACB score) was calculated by evaluating each relevant drug separately.

Covariates for participants on the index date

Demographic attributes (age, gender, and occupation) and medical histories (systemic diseases) were recorded based on the verbal statement of participants, and approximate national electronic database records were reviewed and verified [26].

The overall comorbidity burden was evaluated using the Charlson Comorbidity Index (CCI), which assigns a weighted score to each of 17 possible comorbid conditions based on the relative 1-year risk of mortality [29, 30].

Statistical analysis

Because of its retrospective cohort design, this study only enrolled patients admitted to our hospital within a certain range of dates. Therefore, we conducted post hoc computational power analysis using G*Power 3.1.9.6 and calculated the power (1-b err probe) to be 0.99 with influence quantity of 0.641 with the above-mentioned sample size ($n = 106$).

For calculations, IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA) was used. Normal distribution of the data was evaluated by Shapiro-Wilk test. Normal distributions of numerical variables were expressed as mean ± standard deviation, while those that did not show normal distribution were expressed as median (min-max). For continuous variables, the Student t-test or Mann-Whitney U test was performed as appropriate. Categorical data were compared by performing the chi-square test. The relationship between numerical variables was analysed by conducting Spearman or Pearson correlation analysis. As a result of univariate statistical analysis, the variables determined to be significant at $p < 0.10$ and the clinically significant variables were included in the regression analysis as candidate risk factors. After adjustments were made for age, gender, and comorbidity, the most significant determining factors for the relationship with dry eye were determined by conducting multivariate regression analysis. ACB scores were formulated as the test variable while DED and receiver operating characteristic (ROC) curves were formulated as the state variables, and the diagnostic value of the ACB score was evaluated based on the area under the ROC curve (AUC) (Fig. 1). The optimal cut-off value was determined using the Youden index. Values of $p < 0.05$ were considered to be significant for statistical analysis.

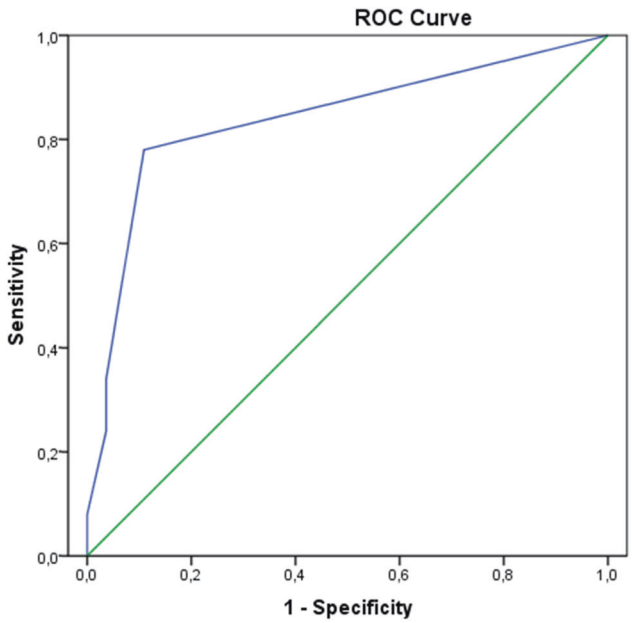

Fig. 1 Roc curve analysis for the estimation of DED.

RESULTS

Among our study population, 60 (11.9%) individuals were diagnosed with DED and 60 participants without known or newly diagnosed eye disease were assigned to the control group. Our study thus enrolled a total of 120 participants. Nine patients diagnosed with DED and five participants from the control group were excluded due to discrepancies or deficiencies in their data or the inability to access their previous records. The mean age of patients diagnosed with DED was 59.0 ± 11.6 years and more than half of these patients ($n = 33$, 64.7%) were women. DED patients had higher CCI scores ($p = 0.01$), lower Schirmer test scores ($p = 0.01$), and higher OSDI scores ($p = 0.01$). In addition, the rate of DED patients with ACB scores of ≥1 (74.0%) was higher than that in the control group (10.9%) ($p = 0.01$). There was no statistically significant difference between the two groups in terms of age and gender. Clinical parameters of the study population are given in Table 1.

The anticholinergic burden in our study population was positively correlated with age ($r = 0.21$, $p = 0.03$), OSDI score ($r = 0.22$, $p = 0.02$), and CCI score ($r = 0.69$, $p = 0.01$), while it was negatively correlated with Schirmer test results ($r = –0.46$, $p = 0.01$) (Table 2).

In univariate logistic regression analysis, significant relationships were found between CCI scores and anticholinergic burden and DED ($p = 0.01$ and $p = 0.01$). Age and female gender, on the other hand, did not reach statistical significance. After adjustment for age, gender, and CCI score (Model 1), anticholinergic burden and CCI score were significantly associated with DED ($p = 0.02$ and $p = 0.02$). Every 1-unit increase in ACB score was found to increase the likelihood of having DED by 2.97 times (Table 3). This model explained 37.4% (Cox and Snell R^2) and 49.9% (Nagelkerke R^2) of the DED variance in the entire group.

ROC curve analyses showed that a cut-off value of 1 for total ACB score was best for the estimation of DED, with sensitivity of 78.0% and specificity of 89.0% (ROC: 0.839 ± 0.042, $p = 0.01.1$).

Table 1. Characteristics of the sample.

Variables	Total ($n = 106$)	Dry Eye Disease		p
		Positive ($n = 51$)	Normal $n = 55$)	
Demographics				
Age (years), mean ± SD	57.4 ± 10.6	59.0 ± 11.6	56.2 ± 9.5	0.17
Gender (female), *n* (%)	65 (61.3)	33 (64.7)	32 (58.2)	0.49
CCI, median (min-max)	1 (0–4)	2 (0–4)	0 (0–3)	**0.01**
Assessment tools				
Schirmer test, mm, mean ± SD	7.8 ± 4.3	3.8 ± 2.4	11.4 ± 1.4	**0.01**
OSDI score, mean ± SD	23.1 ± 16.5	35.3 ± 16.7	12.0 ± 2.1	**0.01**
ACB score, *n* (%)				
0	62 (59.0)	13 (26.0)	49 (89.1)	**0.01**
1+	43 (41.0)	37 (74.0)	6 (10.9)	

CCI Charlson Comorbidity Index, *OSDI* Ocular Surface Disease Index.
Values given in bold indicate statistically significant results ($p < 0.05$).

Table 2. Correlation analysis of the sample.

Variables	Anticholinergic burden		Schirmer test		OSDI score	
	r	*p*	*r*	*p*	*r*	*p*
Age (years)	0.21	**0.03**	−0.17	0.09	0.06	0.54
Anticholinergic burden	-	-	−0.46	**0.01**	0.22	**0.02**
Schirmer test	−0.46	**0.01**	-	-	−0.54	**0.01**
OSDI score	0.22	**0.02**	−0.54	**0.01**	-	-
Charlson Comorbidity Index	0.69	**0.01**	−0.51	**0.01**	0.38	**0.01**

OSDI Ocular Surface Disease Index.
Values given in bold indicate statistically significant results ($p < 0.05$).

Table 3. Association of anticholinergic burden with dry eye disease.

	Unadjusted		Model 1	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.03 (0.99–1.07)	0.18	1.01 (0.95–1.06)	0.84
Gender	0.76 (0.35–1.66)	0.49	0.73 (0.26–2.01)	0.56
Charlson Comorbidity Index	4.40 (2.5–7.72)	**0.01**	2.34 (1.18–4.70)	**0.02**
Anticholinergic burden	6.20 (2.73–14.1)	**0.01**	2.97 (1.22–7.24)	**0.02**

Values given in bold indicate statistically significant results ($p < 0.05$).
Model 1: Adjusted for age, gender, and comorbidities.

DISCUSSION

The effect of anticholinergic drugs on the eyes is a topic that has not been adequately studied among adults. This study showed that taking at least one anticholinergic drug was associated with an approximately threefold increase in the risk of DED in adults. This relationship remained important even after adjustments were made for possible confounding factors such as age, gender, and comorbidities. This finding provides evidence of the risk of DED among people undergoing therapy with drugs possessing anticholinergic properties. We also revealed a negative correlation between the ACB scale and the Schirmer test, as well as a positive correlation between the ACB scale and OSDI score. In addition, more than half of the DED patients in our study population were women, and the prevalence of the disease was found to be 11.9%. These findings were also consistent with previous results reported in the literature [2–4, 31].

As is known, anticholinergic drugs affect the receptors of the lacrimal gland and conjunctival goblet cells, reducing the aqueous and mucous secretions from these cells while increasing the risk of DED [6, 12, 32]. Therefore, an association of anticholinergic drugs with DED would not be surprising. A recent population-based study involving approximately 80,000 participants evaluated drug groups separately and showed that anticholinergic drugs increased dry eye symptoms [9]. However, that study did not involve an evaluation of ACB to show the cumulative effect of anticholinergic drugs [9]. The effects of anticholinergic drugs on the eyes have been studied, but such studies have rarely taken into account the cumulative effect of drugs. Our study, on the other hand, revealed the relationship between anticholinergic burden and dry eye disease more clearly, taking into account the cumulative effect of ACB drugs.

In the literature, many scales have been used to predict the cumulative effect of anticholinergic drugs, but there is a limited number of studies evaluating the scales predicting the effects on the eyes [21]. A recent study evaluating four different anticholinergic burden scales revealed a statistically significant relationship between ACB score and DED in the geriatric population [21]. However, unlike our study, that study did not enrol people under 65 years of age, and it evaluated patients' dry eye complaints only with the Schirmer test [21]. As is known, there are many confounding factors in cases involving elderly patients, such as cognitive status, multiple drug use, and comorbidities in particular, and this can be a problem, especially in studies conducted with this population [33]. In the literature, there are also studies on peripheral and central side effects of ACB administration in younger populations [34]. In a study conducted by Szabo et al. for example, the peripheral side effects of anticholinergic burden were evaluated in a younger population (mean age of 56 years) using the ACB scale, and it was ascertained that an excess of anticholinergic load had a statistically significant effect on peripheral side effects such as fractures and falls [34]. In light of the findings described here, we can say that our study is one of the rare studies evaluating anticholinergic burden, and especially in a younger population, while taking into account all comorbidities.

Many recent studies have shown DED to be associated with many systemic diseases [35–37]. In light of those studies, our study was designed to reveal the relationship between DED and CCI scores, showing the total cumulative effect of comorbidities. In addition to these findings, we showed for the first time that every 1-unit increase in CCI score more than doubled the risk of DED. Therefore, systemic comorbidities such as drug use in people diagnosed with DED should not be ignored. These results also shed light on the importance of embracing a multidisciplinary approach towards ADD patients [38].

Our study has some limitations. First, the drugs used by these patients in the last 3 months were included in the study, but there is a possibility that the patients may not have used those drugs regularly during that period of time. Secondly, because regression analysis was performed with a relatively small group of patients, some covariates are likely to have affected the statistical significance. Therefore, there is a need for larger-scale prospective studies to evaluate the predictive value of ACB in DED.

The strengths of our study were that it was a population-based study with large sample size, and it involved comprehensive clinical and ophthalmologic evaluations. In addition, when we made adjustments for all confounding factors (age, gender, and comorbidities), we found that the significance levels remained the same. We used reliable and verified tools in diagnosing DED and assessing its severity. Finally, we shared real-life data obtained in clinical settings in order to facilitate the conversion of results into routine practice for DED patients.

This study revealed that the cooccurrence of DED and exposure to anticholinergic drugs is not uncommon among adults. In individuals at risk of DED, increased awareness of anticholinergic burden may allow for earlier targeted health interventions. There is a need for future longitudinal studies to recommend strategies such as treatment changes or drug reduction for preventing the risk of dry eye in adults with high anticholinergic burden.

SUMMARY

What was known before

- A series of topical and systemic drugs, have been associated with the signs and symptoms of Dry eye disease. The anticholinergic burden is related to the cumulative effect of one or more drugs that have anticholinergic activity.

What this study adds

- Anticholinergic burden was associated with an approximately threefold increase in the risk of Dry eye disease in adults. It was shown that a negative correlation between the Anticholinergic burden scale and the Schirmer test, as well as a positive correlation between the Anticholinergic burden scale and OSDI score.

DATA AVAILABILITY

The database is available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

Conceptualization: ZK, RNA; Methodology: ZK, RNA; Formal analysis and investigation: ZK, RNA; Writing - original draft preparation: ZK; Writing - review and editing; ZK, Supervision: ZK, RNA.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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