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Research Articles

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PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

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Acknowledgements: Any technical or financial support or editorial contributions (statistical analysis, English/Turkish evaluation) towards the study should appear at the end of the article.

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CONTENTS

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AT A GLANCE

Esteemed colleagues,

In the third issue of 2023, the *Turkish Journal of Ophthalmology* features six original studies, four case reports, and one review.

In their prospective study titled "Contact Lens Use Advice–Risks and Outcomes. Are Patients Drowning in Information but Starved for Knowledge?", Tsatsos et al. assessed the contact lens hygiene awareness levels of 50 consecutive patients presenting to an eye casualty department and investigated the relationship between the type of contact lens used and their contact lens hygiene approach. The study included a high proportion of women, and the most commonly used contact lens type was monthly, followed by daily, bi-weekly, and a small percentage of extended-wear contact lenses. Based on their contact lens hygiene practices, the patients were classified into low-, moderate-, and high-risk groups. Of 25 patients diagnosed with corneal ulcer, 23 were found to have poor contact lens hygiene and these patients had slower visual recovery. The authors concluded that the patients did not have adequate knowledge about contact lens hygiene and emphasized the need for continuing education on this topic.

In their prospective study titled "Comparison of Hybrid Contact Lenses and Rigid Gas-Permeable Contact Lenses in Moderate and Advanced Keratoconus", Yıldız et al. fitted a new-generation hybrid contact lens to 51 patients and a gas-permeable rigid contact lens to 40 patients with moderate and advanced keratoconus and compared their clinical and topographic characteristics. The two groups were similar in terms of age, gender, and keratoconus stage and exhibited no difference in logMAR visual gain. There was a greater increase in vision in patients with central cones with both lens types, and this increase was more pronounced in the group using rigid gas-permeable contact lenses. However, the researchers noted that larger numbers and longer follow-up of keratoconus patients are needed to see the long-term results of hybrid contact lenses.

A study titled "Long-Term Follow-up Results of Primary Canaliculitis Patients", Bayuk et al. retrospectively examined the demographic characteristics, clinical findings, microbiological profiles, and treatment results of 26 patients diagnosed with primary canaliculitis. The patients' most common clinical complaint was epiphora (46.1%), followed by purulent discharge and itching. Many of the patients had been treated for chronic conjunctivitis and the time to diagnosis ranged from 1 to 60 months. Obstruction occurred more frequently in the lower canaliculi and the leading microbial agent was Actinomyces. The authors reported that in patients with canaliculitis, the signs and symptoms improved within one month after canaliculotomy and curettage of the canalicular content, but treatment was delayed because of late diagnosis.

Gür Güngör et al. investigated the role of vascular damage in the pathogenesis of glaucoma in their clinical study titled "Macular and Peripapillary Vascular Densities in Non-Glaucomatous Eyes of Patients with Unilateral Glaucoma". They evaluated optic nerve, peripapillary, and macular vessel densities in both eyes of patients with unilateral glaucoma and controls using optical coherence tomography angiography. There were significant differences in rim area, cup volume, mean cup/disc ratio, and retinal nerve fiber layer thickness in eyes with glaucoma compared to fellow eyes without glaucoma and controls. However, in terms of vascular density, except for the intradisc region, all parameters in the peripapillary and macular regions were lower in glaucomatous eyes while there was no statistically significant difference between fellow eyes without glaucoma and the control group. The researchers stated that the lack of vascular changes in the fellow eyes of unilateral glaucoma patients compared to controls did not support their hypothesis that the vascular pathway may be responsible for the pathogenesis of glaucoma.

In their study titled "Clinical Relevance of Choroidal Thickness in Obese and Healthy Children: A Machine Learning Study", Bulut et al. examined macular and peripapillary choroidal thicknesses with optical coherence tomography in 59 obese and 35 healthy children and evaluated the effectiveness of these parameters in distinguishing obese children from healthy children using the random forest (RF), support vector machine (SVM), and multilayer perceptron algorithms. The study showed that obesity has an effect on choroidal thickness, and the authors reported that both the RF and SVM algorithms were effective and accurate in the classification of obese and healthy children.

Kayhan et al. retrospectively compared inner retinal changes in 74 patients with multiple sclerosis (MS) and 40 healthy individuals in their study titled "Regional Analysis of Inner Retinal Layer Changes in Multiple Sclerosis with and without Optic Neuritis". They found that peripapillary retinal nerve fiber layer (pRNFL), macular retinal nerve fiber layer (mRNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer, and total macular thicknesses were significantly thinner in the MS group. Similarly, MS patients with optic neuritis had significantly thinner

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mean pRSLT, mRSLT, GCL, IPL, and total macular thicknesses than those without optic neuritis, and the GCL and IPL thinning was significantly greater in the inferior subfield. The authors reported that GCL and IPL were a robust and reliable biomarker for MS patients.

The review titled "Applications of Mitomycin C in Cornea and External Disease" by Crespo et al. provides information about the use of MMC in external disease, such as in pterygium surgery, ocular surface neoplasia, and refractive surgery. In addition to its treatment effectiveness, it also draws attention to the potential complications of using MMC, such as endothelial cell loss, corneal perforation, scleral melting, secondary glaucoma, iritis, and endophthalmitis. The authors mention the lack of consensus on MMC treatment protocols for corneal and external disease and discuss applications related to the use of MMC in their review of the relevant literature on this topic.

The first case report of this issue, by Uçakhan Gündüz et al., concerns the surgical treatment of limbal dermoid, a congenital benign tumor, and presents a lamellar keratoplasty technique performed using microkeratome-assisted anterior lamellar graft.

Menteş et al. describe a 65-year-old woman with sudden and severe vision loss in the left eye after receiving the second dose of Pfizer-BioNTech COVID-19 vaccine. They showed by multimodal imaging that the patient developed diffuse paracentral acute middle maculopathy (PAAM) with concurrent acute macular neuroretinopathy.

In a case report by Sedlak et al. titled "Late-Onset Neuromyelitis Optica Spectrum Disorder Mimicking a Non-Arteritic Anterior Ischemic Optic Neuropathy–Case Report", a 60-year-old female patient presenting with painless vision loss and suspected of having ischemic anterior optic neuropathy was found to have aquaporin-4 immunoglobulin G antibody positivity and contrast-enhanced MRI findings of optic nerve and optic chiasm inflammation. As a result, the authors emphasized that the possibility of late-onset neuromyelitis optica spectrum disorder should be considered in the differential diagnosis of ischemic optic neuropathy in older patients.

In a case report by Top Kartı et al., a 43-year-old woman presenting with headache, limited leftward gaze, and muscle weakness on the left side of her face was diagnosed as having eight syndrome secondary to syringomyelia associated with type I Chiari malformation. The authors emphasized that this was the first reported case in which syringomyelia involving the brain stem caused eight syndrome.

We hope that the articles selected for this issue will provide you interesting and enjoyable reading.

Respectfully on behalf of the Editorial Board,

Nilgün Yıldırım, MD

Original Article

Contact Lens Use Advice–Risks and Outcomes: Are Patients Drowning in Information but Starved for Knowledge?

Michael Tsatsos*, Ioannis Athanasiadis*, Cheryl MacGregor**, Suresh Kumar Sharma***, David Anderson**, Parwez Hossain**

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**Southampton University Hospital, Southampton, United Kingdom
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Abstract

Objectives: Microbial keratitis can cause significant visual morbidity and is a common reason for presentation to eye casualty clinics. Contact lens wear and poor contact lens hygiene significantly increase the risk of corneal infection. This study aimed to determine the level of contact lens hygiene awareness amongst contact lens wearers attending our service and determining whether contact lens type and hygiene attitude are related to severity of disease.

Materials and Methods: This prospective questionnaire-based study included 50 consecutive patients attending the eye casualty clinic of a tertiary referral center. Visual acuity was assessed at presentation and 2 weeks after diagnosis. Patients were divided into subgroups according to contact lens type (monthly, bi-weekly, daily, and extended day and night wear) and risk group (low, medium, and high) depending on their contact lens hygiene practices.

Results: Thirty-four women and 16 men were included in this study. Twenty-four patients used monthly disposable contact lenses, 16 used daily disposable contact lenses, 6 were using bi-weekly replacement lenses, and 4 patients were using extended wear (day and night) contact lenses. Twenty-five patients were diagnosed with corneal ulcer, 23 of which had some degree of poor contact lens hygiene. Best corrected visual acuity (BCVA) significantly improved after treatment. Mean BCVA was 0.24 LogMAR before treatment and 0.09 LogMAR after treatment ($p<0.05$).

Conclusion: Our study highlights the need to improve contact lens hygiene awareness and influence hygiene practices. Patients with the poorest contact lens hygiene had slower visual recovery and a higher prevalence of corneal ulcer. Contact lens hygiene advice needs to be clear and reinforced over time.

Keywords: Contact lenses, hygiene, corneal ulcer, infection

Cite this article as: Tsatsos M, Athanasiadis I, MacGregor C, Sharma SK, Anderson D, Hossain P. Contact Lens Use Advice–Risks and Outcomes: Are Patients Drowning in Information but Starved for Knowledge?. Turk J Ophthalmol 2023;53:136-141

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Introduction

Microbial keratitis is a frequent reason for presentations to eye casualty clinics, with an estimated 71,000 new cases per year in the United States and a prevalence of 1.1 per 10,000 in the Netherlands and 0.36 per 10,000 in Scotland.[1,2,3] Microbial keratitis can be mild, with no visual sequelae upon resolution, or it can cause a high degree of morbidity and significant visual loss in up to 14% of cases.[4] Contact lens (CL) wear is a recognized risk factor for infective keratitis and unlike other predisposing factors such as ocular surgery, ocular surface disease, and systemic disease, is modifiable in practice.[5,6,7,8,9,10]

CL wear in itself, irrespective of the CL replacement interval and material, is associated with an increased risk of corneal infection.[9,10] Severe infections that lead to visual loss are more often seen in patients wearing monthly replacement CL rather than in daily disposable CL.[10,11] Other similarly important risk factors implicated in infection are extended wear, overnight wear, poor lens disinfection, and poor CL hygiene.[7,8,9,10,11,12]

Poor CL hygiene is a known contributor to microbial keratitis.[7,8,9,10,11,12,13] In a study by Brewitt[13] 66% of complications observed in CL wearers were attributed to poor hygiene practices.

To assess levels of patient CL hygiene awareness and adherence, we conducted a prospective study examining the level of CL hygiene awareness in patients attending an eye casualty clinic and the effect of their CL hygiene practices on visual acuity (VA) and presenting pathology.

Materials and Methods

We prospectively analyzed 50 consecutive patients with CL-related complaints presenting to the eye casualty of our tertiary center over a period of 2 months. Informed consent was obtained from all patients and the study adhered to the tenets of Helsinki (ethical approval number: 07/H0512/39).

After ophthalmic examination in eye casualty by a member of the corneal service, an independently validated questionnaire was used to identify the type and length of CL use, source of CL purchase (optician or internet), CL hygiene behavior, and CL hygiene advice received. Patients were specifically asked whether they showered, slept, or swam in their CLs and whether they recalled receiving advice regarding CL hygiene. The patients were examined on presentation and 2 weeks later by the corneal team and in the interim were assessed for response to treatment by the eye casualty team.

In tertiary centers, patients with CL-related problems are often referred after initiation of treatment by local ophthalmologists. In our cohort, empirical treatment was started or continued solely or in addition to our regimen and thus we did not discontinue previous treatment in order to take corneal cultures/scrapes.

Patients were subdivided into three groups on the basis of their CL risk behaviors. The high-risk group was defined as patients who engaged in all three components of risk behavior (slept, showered, and swam in CLs). The medium-risk group was defined as patients who engaged in two of the above risk behaviors, and those in the low-risk group reported engaging in only one of the risk behaviors.

The patients' responses were compared against the CL leaflets frequently used by our optometry department (from CL manufacturers no. 7, David Thomas, Ultravision, Synergeyes, and Mark'ennovy).

Statistical Analysis

The data was analyzed using statistical software SPSS version 19 (IBM, SPSS, Chicago, IL, USA). Sample normality was confirmed with the Shapiro-Wilk test. The association with VA data was analyzed using one-way analysis of variance (ANOVA) for CL type and risk behavior and t-test for diagnosis.

Results

Demographics and Contact Lens Types

The study included 50 consecutive patients (34 female, 16 male) who were regular CL wearers. The mean age was 38 years (range, 16 to 65 years). All patients had been using CLs for over a year. The patients most commonly used monthly replacement CLs (n=24; Table 1) and were in the medium-risk group (n=23; Figure 1). Forty-nine patients bought the CLs solely from a local optician. One patient bought their CLs over the internet but had previously purchased them from an optician. Patient demographics and contact lens types are detailed in Table 1.

Best corrected visual acuity (BCVA) showed marked improvement after treatment. Mean pre-treatment VA was 0.24 LogMAR and improved to 0.09 LogMAR after initiation of treatment. The difference between pre-treatment and 2-week follow-up BCVA in the cohort was statistically significant ($p<0.05$). When compared according to patient behavior (high risk, medium risk and low risk), we observed that VA improved significantly following treatment in the medium and low-risk groups ($p=0.017$ and 0.002, respectively). However, in the high-risk group, the improvement in VA was not statistically significant ($p=0.053$) (Figure 1).

In one-way ANOVA, there was no difference in VA before or after treatment according to CL type except for extended wear CLs, which were associated with significantly worse VA (Table 2 and Figures 2, 3).

Contact Lens Hygiene Advice and Practices

Table 3 outlines the patients' recall of CL hygiene advice received and their corresponding CL hygiene practices. The majority of patients in the study (n=31) did not recall receiving

Table 1. Patient demographics and contact lens types

Gender		
All	**Male**	**Female**
50	16	34
Age (years)		
	Mean	**Range**
	38	16-65
Contact lens type		
	n	**Percentage**
Monthly replacement	24	48%
Daily disposable	16	32%
Bi-weekly replacement	6	12%
Extended wear (day and night)	4	8%

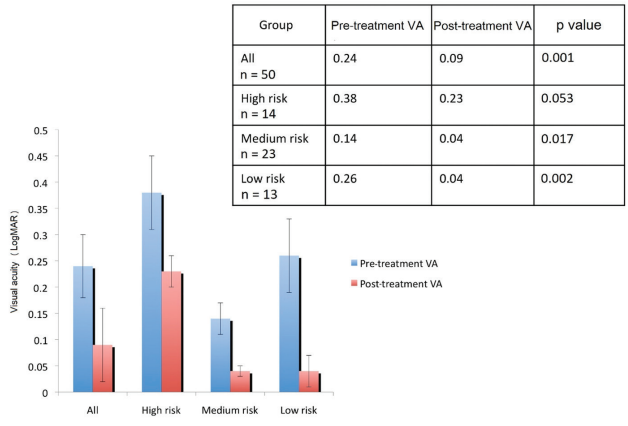

Figure 1. Best corrected visual acuity (BCVA) before and after treatment

any CL hygiene advice, and most patients were not aware that showering in CLs is not advised.

Diagnosis

Twenty-five out of the 50 patients were diagnosed with a corneal ulcer, whereas the remaining 25 patients were diagnosed with less severe CL-related problems such as corneal abrasion and superficial punctate erosions. In the latter group, 2 of the patients presented with corneal infiltrates. Solely for the purpose of comparing visual acuity, these patients were grouped with the corneal ulcer patients under the label of microbial keratitis.

Of the 25 patients diagnosed with corneal ulcer, 12 (48%) used monthly disposable CLs and 8 (32%) used daily disposable CLs. All 4 patients wearing extended wear (day and night) CLs were diagnosed with corneal ulcer. Of these 25 cases, 11 patients (44%) were in the high-risk group. Two patients (8%) were in the low-risk group and the remaining 12 patients belonged to the medium-risk group (Figure 4).

Initial and final VA showed no statistical difference between patients with microbial keratitis (including the 25 cases with corneal ulcers and the 2 cases with corneal infiltrates due to the clinical appearance) and those with other minor adverse complications (Table 4a-b).

Content of Contact Lens Leaflets

Advice on showering and swimming in CLs was absent in 3 of the 5 leaflets. Three out of the 5 leaflets contained advice about sleeping in CLs and mentioned a recommended time limit of daily wear. All leaflets mentioned hand washing. Three leaflets were particularly difficult to read and extract information from.

Discussion

The role of CL wear, particularly when associated with poor CL hygiene is a well-studied and recognized risk factor for infective keratitis.[9,10] Despite this, conveying the importance of good CL hygiene to CL wearers continues to be a challenge, and CL-related keratitis remains an important cause of visual morbidity.[9,10,11] Visual outcome is determined by numerous factors, including virulence of the organism, severity of keratitis at the time of presentation, and promptness to initiate appropriate treatment.[4] There is a spectrum of causative organisms and trends vary between climates. In Europe, *Pseudomonas aeruginosa* is the most commonly identified pathogen amongst CL wearers, followed by gram-positive organisms.[14,15] Although *Acanthamoeba* is an important pathogen of severe CL keratitis, cases of Acanthamoeba keratitis remain rare. *P. aeruginosa* is able to adhere to and colonize CL materials during CL wear, can survive in CL storage cases, and has resistance to CL disinfectants.[16] *Acanthamoeba* are free-living cyst-forming ubiquitous protozoa found in air, dust, soil, and fresh water. They are highly resistant to disinfection with chlorine and are thus not eradicated from tap water.[16,17,18] For this reason, showering with, swimming with, and washing CLs in fresh water are regarded as risk behaviors.

In addition to the heightened risk of infective keratitis associated with CL wear, factors such as wearing CLs for long periods, overnight CL use, and poor hygiene play a major role in further increasing the risk.[4,5,6,7,8,9,13] In our study, 62% of patients were unaware of CL hygiene recommendations. Patients in the high-risk group had a higher prevalence of corneal ulcer and worse VA at presentation that did not improve significantly at 2-week follow-up, whereas in the medium and low-risk groups, vision had recovered significantly at 2-week follow-up (Figure 1). This high-risk group had greater visual morbidity as a result of their keratitis, which was also slower to resolve.

Dividing the patient cohort into two groups according to diagnosis (microbial keratitis vs. less severe non-infective keratitis pathology) revealed no difference in final visual outcome. There were also no statistically significant differences in presenting or final BCVA between daily, bi-weekly and monthly CL users. However, both presenting and final BCVA were significantly worse in extended wear CL users.

The patients' low level of hygiene compliance along with the low recall rates of information provided by their opticians when buying their CLs suggest that patient education and understanding of the potential risks associated with CL wear need to be improved. Among the patients who did recall

Table 2. Extended wear contact lenses exhibited worse outcome than all other types of contact lenses for both initial and final visual acuity (VA)

Multiple comparisons							
Scheffe							
Dependent variable			**Mean difference (I-J)**	**Std. error**	**p-value**	**95% confidence interval**	
						Lower bound	**Upper bound**
Initial VA	Extended	Monthly	0.85750*	0.20061	0.001	0.2754	1.4396
		Bi-Weekly	0.90833*	0.23977	0.006	0.2126	1.6041
		Daily	1.07500*	0,20765	0.000	0.4724	1.6776
Final VA	Extended	Monthly	0.68792*	0.21842	0.028	0.0541	1.3217
		Bi-Weekly	0.74833	0.26106	0.050	-0.0092	1.5059
		Daily	0.68313*	0.22608	0.038	0.0271	1.3392

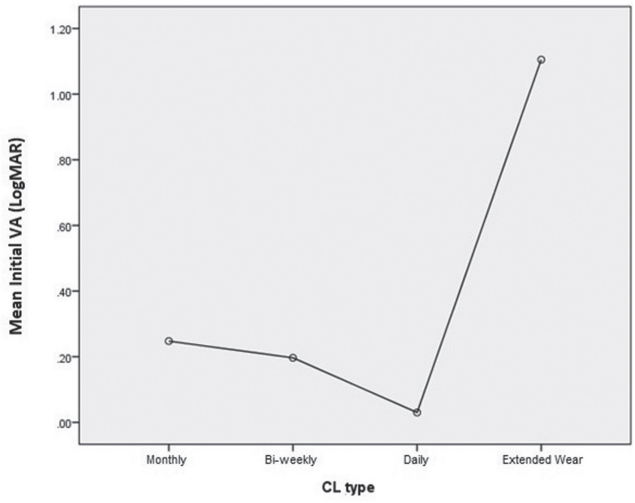

Figure 2. Plot of mean initial LogMAR visual acuity (VA) according to contact lens (CL) type

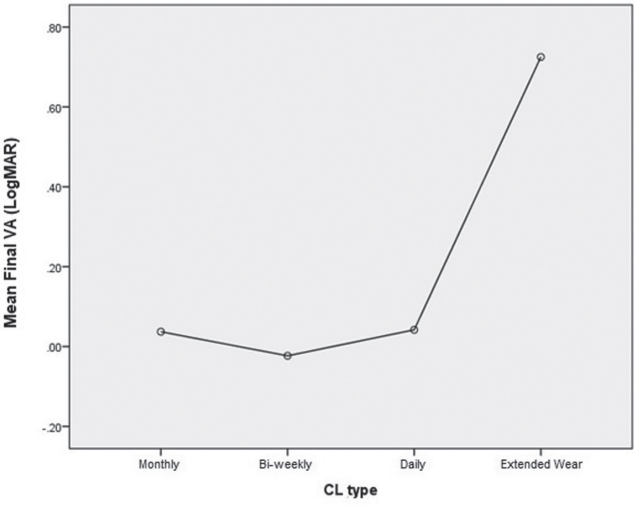

Figure 3. Plot of mean final LogMAR visual acuity (VA) according to contact lens (CL) type

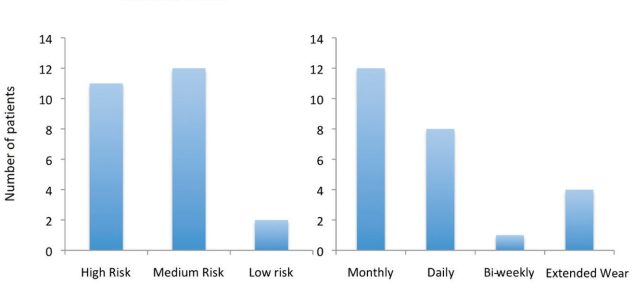

Figure 4. Distribution of corneal ulcer diagnoses according to risk behavior category and contact lens (CL) type

Table 3. Patient recall of contact lens (CL) hygiene advice and risk behavior

Advice recall	n	%
No advice recalled	31	62%
Some advice recalled: Avoid sleeping in CL Avoid swimming in CL Avoid showering in CL	7 6 1 0	12%
All advice recalled	12	24%
Risk behavior		
Sleeping in CL	16	32%
Showering in CL	33	66%
Swimming in CL	27	54%
Patients who recalled all CL hygiene advice (n=12)		
No risk behaviors (good CL hygiene)	7	
Sleeping in CL (moderate CL hygiene)	1	
Showering in CL (moderate CL hygiene)	1	
All risk behaviors (poor CL hygiene)	3	

receiving CL hygiene advice, there was 58% compliance with the advice given. This highlights that patient education can influence CL practices and there is clearly potential to increase compliance with further education. In our study there was a strong link between poor CL hygiene and increased visual morbidity, where patients with the poorest CL hygiene had worse presenting vision and a slower visual recovery.

An interesting finding from this study was that a large proportion of patients (48%) wore monthly CLs (removed daily, replaced monthly), demonstrating the commercial prevalence of monthly CLs. Daily disposable CLs have not been found to reduce the risk of infective keratitis, but studies have indicated that patients are less likely to incur severe visual loss, thus suggesting less severe keratitis.[10,11] In our study, a higher proportion of monthly CL wearers were diagnosed with corneal ulcer than those who wore daily CL, suggesting a link between the severity of corneal infection and the type of CL used, consistent with the literature.

Of the patients presenting with corneal ulcer, 92% had poor CL hygiene practice to some degree (44% were in the high-risk and 48% in the medium-risk behavior group). All patients using extended wear CLs (day and night wear, replaced monthly) presented with a corneal ulcer rather than an epithelial defect or other diagnosis. Patients wearing extended wear CLs also had poor CL hygiene (sleeping and showering in CL), a finding that supports previous literature linking poor CL hygiene and extended CL wear to corneal infection.

The guidelines on CL hygiene advice are a contentious topic, particularly as CL wear is often commenced outside of the hospital setting, but infections or problems associated with CLs often are seen by an ophthalmologist in eye casualty. Although the Royal College of Optometrists provides guidance on CL use, our study suggests that CL hygiene advice needs to

Table 4a. No statistical difference in visual acuity (VA) before or after treatment according to diagnosis					
Group statistics					
Diagnosis		**No. of patients**	**Mean**	**Std. deviation**	**Std. error mean**
Initial VA	Microbial keratitis	27	0.2704	0.59716	0.11492
	Others	23	0.2052	0.18263	0.03808
Final VA	Microbial keratitis	27	0.1207	0.58927	0.11340
	Others	23	0.0461	0.10003	0.02086

Table 4b. No statistical difference in visual acuity (VA) before or after treatment according to diagnosis										
		Levene's test for equality of variances		**t-test for equality of means**						
		F	**Sig.**	**t**	**df**	**p-value**	**Mean difference**	**Std. error difference**	**95% confidence interval of the difference**	
									Lower	**Upper**
Initial VA	Equal variances assumed	2.558	0.116	0.503	48	0.617	0.06515	0.12955	-0.19532	0.32563
Final VA	Equal variances assumed	2.181	0.146	0.599	48	0.552	0.07465	0.12455	-0.17577	0.32508

be given priority and reinforced over time, as it appears to be inadequate to provide this information only once during the CL sale transaction. Another cause of concern is the possibility of purchasing CLs over the internet. Although not a popular option in our patient cohort, internet purchases pose a threat to patient education, as this domain is difficult to regulate and guidelines are difficult to enforce. This option may be preferred because it is convenient and frequently cheaper than acquiring CLs through local opticians or an ophthalmic practitioner. However, during this speedy transaction consumers could easily overlook the CL hygiene information that is normally given during a face-to-face consultation. As the COVID pandemic still looms and travel/retail restrictions exist at the time of writing, internet retailers would ideally make sure that patients purchasing CLs online read all the important hygiene information in short, simple, and user-friendly sites.

Study Limitations

A limitation of this study is that the results are based on 50 consecutive patients that presented as an emergency to an eye casualty clinic within a period of 2 months and thus there was no control group. Our study helps to identify and elucidate the problem of continuing patient education and the feeling of complacence some people develop after a long period of CL use. Although even the strictest adherence to CL manufacturers' guidelines would not completely eliminate all corneal infections in all CL users, improvement in patient adherence to CL hygiene recommendations appears to be associated with improved visual outcome in case of a successfully treated infection. This message alone should be a great incentive for CL hygiene adherence and could be used by CL practitioners and in patient information leaflets and websites.

Conclusion

It seems clear that there is a need to improve patient CL hygiene awareness. It appears that internet purchases have yet to soar in popularity, suggesting that opticians remain at the center of patient education. It may be beneficial for ophthalmologists to liaise more closely with opticians to reinforce the recommendations of CL hygiene and make them aware of the emergency services available. Additionally, CL wearers should be made aware of the risks associated with CLs and encouraged to reduce those risks with good CL hygiene. CL information materials should offer advice on the importance of CL hygiene, avoidance of sleeping in CLs, and when to seek medical assistance. As poor CL hygiene is an important and well-established risk factor for the development of infective keratitis, it is essential that careful CL hygiene is stressed in information leaflets and by CL fitters and vendors. Perhaps more stringent guidelines are needed, but firstly we need to re-think the way CL hygiene advice is given and reinforced.

Ethics

Ethics Committee Approval: The study adhered to the tenets of Helsinki (ethical approval number: 07/H0512/39).

Informed Consent: Informed consent was obtained from all patients.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: M.T., I.A., C.M., S.K.S., D.A., P.H., Design: M.T., I.A., C.M., S.K.S., D.A., P.H., Data Collection or Processing: M.T., I.A., C.M., S.K.S., D.A., P.H., Analysis or Interpretation: M.T., I.A., C.M., S.K.S., D.A., P.H., Literature Search: M.T., I.A., C.M., S.K.S., D.A., P.H., Writing: M.T., I.A., C.M., S.K.S., D.A., P.H.

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Original Article

Comparison of Hybrid Contact Lenses and Rigid Gas-Permeable Contact Lenses in Moderate and Advanced Keratoconus

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Abstract

Objectives: We aimed to compare the clinical results and topographic data of the new generation hybrid contact lens (HCL) and rigid gas-permeable contact lens (RGPCL) in patients with moderate and advanced keratoconus.

Materials and Methods: In this prospective study, HCL users comprised group 1 and RGPCL users comprised group 2. Snellen uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), and lens-corrected visual acuity (LCVA); manifest spherical-cylindrical values; corneal topography measurements (flat keratometry [K1], vertical keratometry [K2], mean K, maximum K [K_{max}], central corneal thickness [CCT], and thinnest corneal thickness [TCT]); and cone location were recorded.

Results: The study included 83 eyes of 51 patients in group 1 and 61 eyes of 40 patients in group 2. The groups were similar in age and gender ($p>0.05$). Mean LCVA (logMAR) was significantly lower than BCVA in both groups ($p<0.001$). The mean visual gain with contact lenses (Snellen chart) was 3.4±1.8 lines in group 1 and 4.0±2.1 lines in group 2. There was no significant difference between the two groups in BCVA, LCVA, or lines gained ($p>0.05$). There was also no significant difference between the two groups in terms of keratoconus stages, mean K_{max}, CCT, TCT, or cone location ($p>0.05$), while mean UCVA (logMAR) and mean K were higher in group 2 ($p<0.05$). In both groups, the visual gain with lenses was higher in eyes with central cones, and there was significantly greater visual increase in group 2 ($p=0.039$).

Conclusion: In moderate and advanced keratoconus, HCLs improved vision as much as RGPCLs and both lenses were more effective for central cones. Nevertheless, longer term of follow-up and larger numbers of patients are needed for long term follow-up results of HCL.

Keywords: Rigid gas-permeable contact lens, hybrid contact lens, keratoconus

Introduction

Keratoconus is a bilateral, asymmetric, progressive ectatic disease characterized by steepening and thinning of the cornea.[1,2] In keratoconus, stromal thinning and steepening alter the refractive properties of the cornea and cause irregular astigmatism that cannot be corrected with glasses. Because of the irregular astigmatism, contact lens fitting for keratoconus patients requires time and patience on the part of both patient and physician. Nevertheless, keratoconus lenses are preferred because they improve vision beyond what can be achieved with glasses and even help patients avoid surgical treatment options. Therefore, soft or rigid contact lenses are recommended before surgery to provide visual rehabilitation, especially for patients with moderate to advanced keratoconus.[3]

Keratoconus lenses offer visual rehabilitation by providing a new optical surface, either through contact with the cornea or by masking irregularities with the tear film between the cornea and the lens. Although options vary according to disease stage, there are currently five different types of contact lenses for keratoconus patients. The first of these are rigid gas-permeable contact lenses (RGPCLs), which have been used for decades. Soft toric lenses, hybrid contact lenses (HCLs), scleral lenses, and custom-made keratoconus lenses have also been introduced into clinical practice in addition to RGPCLs.[4,5] Soft contact lenses are especially effective in early to moderate keratoconus, while RGPCLs, HCLs, and scleral contact lenses are more

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effective in moderate to advanced keratoconus.[6,7] According to the Global Keratoconus Consensus in 2015, RGPCLs are the first option for patients who are unable to achieve adequate vision and comfort with glasses or contact lenses.[8] However, some patients cannot tolerate these lenses.[7,9,10,11] HCLs were first produced in the 1980s to combine the comfort of soft lenses and the effectiveness of RGPCLs.[12] Due to complications related to the design and low oxygen permeability of the first HCLs, next-generation HCLs were produced in the 2010s. These next-generation HCLs have high oxygen permeability and consist of a rigid lens material that corrects central corneal irregularity and a soft lens material that provides peripheral comfort and lens centration. The SynergEyes KC (SynergEyes Inc., Carlsbad, CA, USA) was the first of the next-generation HCLs and was followed by the ClearKone (Paragon Vision Sciences, Mesa, AZ, USA), UltraHealth (SynergEyes, Inc., Carlsbad, CA, USA), AirFlex (SwissLens, Prilly, Switzerland), and Eyebrid Silicone (Laboratoire LCS; France) HCLs. In the AirFlex HCL, the rigid gas-permeable material is Roflufocon D and the surrounding soft lens material is silicone hydrogel (Filcon V3). It has a spherical, front/back bitoric design, blocks ultraviolet light, and has high oxygen permeability (central Dk: $100x10^{-11}$, peripheral Dk: $50x10^{-11}$ (cm^2/s) x ($mLO^2/[mL \times mmHg]$). The water content is 50%. The rigid lens has a base curve ranging from 5.50 to 10.00 mm (0.05 mm steps) and a diameter of 8.5 mm for irregular corneas and 10.0 mm for regular corneas. The total diameter is 14.9-15.50 mm and the central thickness is 0.20 mm. There are four options for the skirt curve: very flat (J +1.0), flat (J +0.5), standard (J 0.0), and steep (J -0.5).

In this study, we aimed to compare the clinical results and topographic data of the next-generation AirFlex HCL and the Rose K2 RGPCL in patients with moderate to advanced keratoconus.

Materials and Methods

This prospective study was conducted in the Cornea Unit of the Ankara Bilkent City Hospital Clinic of Ophthalmology and adhered to the principles of the Declaration of Helsinki. Ethics committee approval for the study was obtained from the Clinical Research Ethics Committee of the Ankara Yıldırım Beyazıt University Faculty of Medicine. Patients fitted with the AirFlex HCL (SwissLens, Prilly, Switzerland) and Rose K2 RGPCL (Menicon, Co., Ltd., Nagoya, Japan) in our clinic for the treatment of keratoconus were included in the study. Written informed consent was obtained from all patients.

The diagnosis of keratoconus was made in the presence of at least one of the clinical findings (Munson's sign, scissor reflex on retinoscopy, corneal thinning, Fleischer ring, striae of Vogt, prominent corneal nerves, Rizzutti's sign) and with corneal tomography (Sirius® Scheimpflug tomography, Italy).[13] Patients with moderate and advanced keratoconus who had a visual gain of at least two lines on the Snellen chart with the HCL or RGPCL and used these lenses for at least 6 months (at least 8 hours per day) were included in the study. Patients with BCVA of 0.6 decimal or higher on the Snellen chart; those with hard contact lens use in the last month or soft contact lens use in the last week; those who were in the first 6 months of collagen cross-linking (CXL) treatment; those with progression of keratoconus, history of herpetic keratitis, topical drugs use, keratitis, dry eye, blepharitis, glaucoma, and macular or optic disc disease that would affect vision; and those who did not attend regular follow-ups were excluded from the study. Contact lens fitting was performed by the same experienced ophthalmologist. Maximum keratometry (Kmax) values of 47 diopters (D) or less were evaluated as mild, 47-52 D as moderate, and 52 D or more as advanced keratoconus.[14] Cone location was classified as central for cones within the central 3 mm area in the anterior corneal tangential curvature map on corneal topography and paracentral for those outside this area.[15]

Before lens use, all patients' uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), manifest sphere and cylinder values (Topcon KR 8000 Autorefractor Keratometer), biomicroscopic anterior segment and fundus examination findings, and corneal topography measurements (flat keratometry [K1], steep keratometry [K2], mean keratometry [K_{mean}], K_{max}, cone location, central corneal thickness [CCT], and thinnest corneal thickness [TCT]) were recorded. After lens fitting, patients were scheduled for follow-up at 1 week, 1 month, and every 3 months thereafter. Lens-corrected visual acuity (LCVA) at final follow-up, complications associated with contact lens use, lens parameters, and lens use durations were recorded.

Lens Fitting Procedure

AirFlex HCL fitting was done based on the manufacturer's instructions. In the first lens trial for keratoconus patients, a lens base curve 0.2 mm flatter than the patient's Kmean and the standard skirt curve (J 0.0) is used. The lens is put in place using a special applicator with the patient sitting upright or with the head tilted forward and face parallel to the floor. It is very important not to put pressure on the patient's eye during the initial fitting. Applying pressure to the eye may negatively affect both comfort and vision. After 30 minutes, sodium fluorescein is instilled and the patients are examined under cobalt blue lamp at a 30° angle to the biomicroscope. Three main points are considered when evaluating the lens. The first is lens centration; the lens must cover the entire cornea. With HCLs, lens centration is provided by the soft skirt that extends from sclera to sclera. The second point is lens movement. As with soft contact lenses, the movement of the lens ensures tear exchange beneath the lens. With each blink, lens movement of 0.3-0.4 mm is desired. If the lens is tight, the base curve is flattened/increased, and if it is loose, the basic curve is steepened/decreased. If lens centration or movement is still not as desired, the skirt curve is changed. Steepening the lens skirt curve prevents the lens from adhering to the ocular surface and increases lens movement, while flattening reduces lens movement. A tight

lens fitting will not allow for tear exchange beneath the lens and thus may cause corneal edema and limbal vascularization with prolonged use. The third point is fluorescein staining pattern. Unlike the previous vault-based HCLs, full contact between the AirFlex HCL and cornea or minimal fluorescein pooling (0.07-0.10 mm) in the center is desired. This enables assessment with a biomicroscope, as with soft contact lenses. If there is excessive fluorescein pooling in the center, the base curve of the lens is flattened. There should be a fluorescein band (communication for tear exchange) of 1-2 mm around the rigid lens component. If this band is less than 1 mm wide, it indicates a steep lens and the base curve should be increased by 0.1 mm; a band wider than 2 mm indicates a flat lens and the base curve should be reduced by 0.1 mm. Anterior segment images of the HCL fitted to a patient with advanced keratoconus are shown in Figure 1. The Rose K2 is a RGPCL made of Menicon Z. It has an aspheric surface, Dk value of $163x10^{-11}$ (cm^2/s) x ($mLO^2/[mL \times mmHg]$), back optic zone radius (BOZR) of 4.30-8.60 mm, and diameter of 7.90-10.40 mm. It is designed with standard, flat, or steep edge lift. According to the manufacturer's instructions for fitting the Rose K2, the first lens is selected with a BOZR 0.20 mm steeper than the Kmean and is applied to the eye. After 30 minutes, sodium fluorescein is instilled and the patients are examined under cobalt blue lamp at a the biomicroscope. Lens centration, movement, and fluorescein staining pattern are examined. Although a three-point contact pattern is more preferred in fluorescein staining, the BOZR is flattened/increased or elevated/decreased at 0.1 mm intervals until apical contact or two-point contact (apical gap/peripheral contact) is achieved.[4,16] Finally, corneal staining is evaluated with fluorescein drops after removing the lenses. Anterior segment images of the RGPCL fitted to a patient with advanced keratoconus are shown in Figure 2. For both lenses, after determining the appropriate parameters, lens refraction is performed with an autorefractometer. If the values measured by autorefractometer over the contact lens are above 4 D, the vertex calculation is included and the spherical power of the contact lens is determined. In the lens prescription, the base curve, total lens diameter, skirt curve, spherical power, and lens brand are recorded.

Statistical Analysis

The data were recorded and analyzed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 12.3 (MedCalc Software bvba, Ostend, Belgium). Normality of data distributions were analyzed using Kolmogorov–Smirnov test. The data were expressed as mean and standard deviations. Chi-square, paired-samples t, Mann-Whitney U, and Kruskal-Wallis tests were used for data comparisons. Analyses were performed with a 95% confidence interval and a p value less than 0.05 was considered statistically significant.

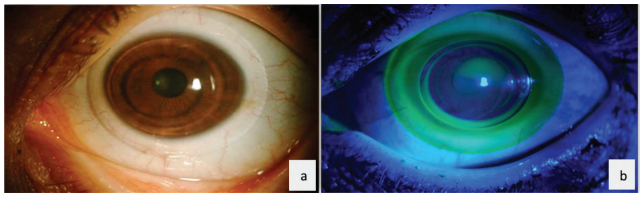

Figure 1. Anterior segment biomicroscopic image (a) and cobalt blue fluorescein staining pattern (b) of an AirFlex hybrid contact lens on the left eye of a patient with advanced keratoconus

Results

The study included 144 eyes of 91 patients. Those who used HCLs were in group 1 (83 eyes of 51 patients) and those who used RGPCLs were in group 2 (61 eyes of 40 patients). The mean duration of lens use was 15.63±9.4 months in group 1 and 14.39±8.8 months in group 2 (p>0.05). The demographic characteristics and manifest refraction values of all patients are presented in Table 1. The two groups were similar in terms of age and sex (p>0.05, Table 1). Manifest cylinder values were significantly higher in group 2 (p=0.023, Table 1). The mean logMar UCVA, BCVA, and LCVA values and topographic data of all patients are shown in Table 2. While there was no significant difference between the two groups in mean BCVA, LCVA, or Snellen lines gained with lenses (p>0.05, Table 2), mean UCVA was significantly higher in group 2 (p=0.004). There was no significant difference between the two groups in terms of mean Kmax, CCT, TCT, cone location, or keratoconus stages (p>0.05, Table 2). Kmean values were significantly higher in group 2 (p=0.039, Table 2). In both groups, the mean logMAR LCVA was lower than BCVA (p<0.001). The mean visual gain on Snellen chart with contact lenses was 3.4±1.8 lines in group 1 and 4.0±2.1 lines in group 2 (p=0.067) (Table 2). None of the patients had limbal vascularization, corneal edema, or keratitis associated with contact lens use.

Figure 3 shows the mean logMAR vision levels of groups 1 and 2 according to keratoconus stage. In group 1, patients with moderate and advanced keratoconus did not differ in mean UCVA (p=0.205) or LCVA (p=0.711), while mean BCVA was significantly higher in patients with advanced keratoconus than in patients with moderate keratoconus (p=0.046). In group 2, there was no significant difference in mean UCVA values between moderate and advanced keratoconus patients (p=0.260), while BCVA and LCVA were significantly higher in patients with advanced keratoconus (p=0.029 and p=0.012, respectively). In both groups, mean LCVA values were significantly lower than BCVA values for both keratoconus stages (p<0.001 for all) (Figure 3).

Figure 4 shows the logMAR visual acuity levels of groups 1 and 2 according to cone location. In group 1, there was no significant difference in mean UCVA and LCVA values between patients with central and paracentral cones (p=0.146 and p=0.733, respectively). The mean BCVA was significantly higher in group 1 patients with central cones (p=0.024). In group 2, the mean UCVA and BCVA values were significantly higher in patients with central cones (p=0.012, p=0.010, respectively), while there was no significant difference in mean LCVA between patients with central and paracentral cones (p=0.533) (Figure 4).

Table 1. Demographic characteristics and manifest refraction values of groups 1 and 2			
	Group 1 (HCL)	**Group 2 (RGPCL)**	***p***
No. of patients/eyes	51/83	40/61	
Age (years)	25.76±5.80	25.80±6.14	0.857¶
Gender (F/M)	17 (33%)/34 (67%)	15 (37%)/25 (63%)	0.423†
MR sphere value (D)	-2.48±3.0	-3.30±3.4	0.100*
MR cylinder value (D)	-2.60±1.2	-3.25±1.5	0.023*
MRSE (D)	-3.79±2.94	-4.96±3.54	0.053*
Collagen crosslinking, yes/no (%)	68 (82%) / 15 (18%)	55 (91%) / 6 (9%)	0.479†

HCL: Hybrid contact lens, RGPCL: Rigid gas-permeable contact lens, MR: Manifest refraction, D: Diopters, MRSE: Manifest refraction spherical equivalent. ¶Paired-samples t-test, †Chi-square test, *Mann-Whitney U test

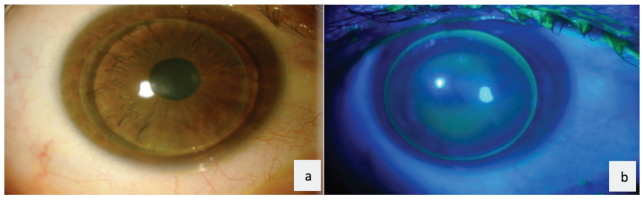

Figure 2. Anterior segment biomicroscopic image (a) and cobalt blue fluorescein staining pattern (b) of a Rose K2 rigid gas-permeable contact lens on the right eye of a patient with advanced keratoconus

Table 2. Vision levels and topographic data of groups 1 and 2			
	Group 1 (HCL)	**Group 2 (RGPCL)**	***p***
UCVA (logMAR)	0.69±0.43	1.0±0.38	0.004*
BCVA (logMAR)	0.30±0.29	0.34±0.27	0.370*
LCVA (logMAR)	0.09±0.10	0.08±0.08	0.380*
Visual gain with lens (Snellen lines)	3.4±1.8	4.0±2.1	0.067¶
K_{mean} (D)	48.24±3.9	49.86±4.6	0.039*
K_{max} (D)	57.55±6.4	59.03±8.3	0.327*
CCT (µm)	413±55	411±49	0.892*
TCT (µm)	407±61	395±51	0.197¶
Cone location (central/paracentral)	62 (75%)/21 (25%)	51 (86%) 10 (14%)	0.063†
Moderate keratoconus Advanced keratoconus	27 (32%) 56 (68%)	16 (26%) 45 (74%)	0.265†

HCL: Hybrid contact lens, RGPCL: Rigid gas-permeable contact lens, UCVA: Uncorrected visual acuity, BCVA: Best corrected visual acuity, LCVA: Lens-corrected visual acuity, Kmean: Mean keratometry value, D: Diopters, K_{max}: Maximum keratometry value, CCT: Central corneal thickness, TCT: Thinnest corneal thickness, KC: Keratoconus. *Mann-Whitney U test, ¶Paired-samples t-test, †Chi-square test

The mean visual gain on Snellen chart with contact lenses (difference between BCVA and LCVA) in patients with central and paracentral keratoconus was 0.36 and 0.28 lines in group 1 (p=0.135) and 0.43 and 0.20 lines in group 2 (p=0.003), respectively. The visual gain in patients with central cones was significantly greater in group 2 than in group 1 (p=0.039).

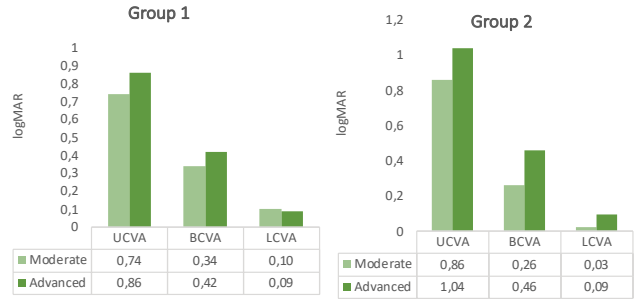

Figure 3. Vision levels in groups 1 and 2 according to keratoconus stage
UCVA: Uncorrected visual acuity, BCVA: Best corrected visual acuity, LCVA: Lens-corrected visual acuity

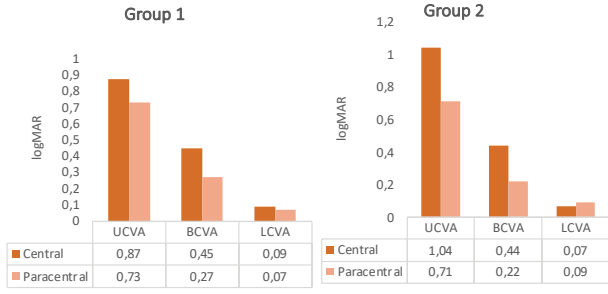

Figure 4. Vision levels in groups 1 and 2 according to cone location
UCVA: Uncorrected visual acuity, BCVA: Best corrected visual acuity, LCVA: Lens-corrected visual acuity

Discussion

Keratoconus is a serious corneal disease that is more prevalent in young patients, can progress if left untreated, and results in corneal transplantation surgery when glasses or contact lenses do not provide sufficient visual improvement. As most keratoconus patients are young, it leads to serious psychological problems and job loss. Today, with the widespread use of modern corneal topographers, keratoconus patients are diagnosed earlier than in the past, and treatment with CXL halts progression of the disease. However, untreatable advanced keratoconus, the formation of corneal haze after CXL, and irregular corneas following penetrating keratoplasty, intracorneal rings, and Excimer laser surgery also occur at a substantial rate. Here, rigid contact lenses

(RGPCLs, HCLs, scleral contact lenses) provide a healthy optical surface either by contact with the cornea or by the masking effect of the tear film between the cornea and lens, which eliminates corneal irregularities and provides visual improvement.[17]

Contact lens fitting in keratoconus patients is a tedious process for both practitioner and patient because of the irregular shape of the cornea. Therefore, it is important to decide which lens to start with for keratoconus patients. All keratoconus lenses have their own advantages and disadvantages.[8] Customized soft toric lenses provide greater comfort than other lenses but have a limited effect on irregular corneas.[18] Therefore, they are preferred in early keratoconus.[6] RGPCLs are used most commonly for keratoconus. RGPCLs provide significant visual gain by reducing corneal irregularities and higher-order aberrations. However, these lenses cannot be tolerated by some patients due to hypertrophic scarring, erosion, and epithelial damage after apical contact with the cornea.[4,8,19] The apical contact approach in RGPCL fitting utilizes a large diameter lens and flat base curve, but this may cause corneal epithelial erosion and apical hypertrophic scar.[20] A smaller lens diameter and steep base curve provides an apical vault, thereby reducing the complications associated with rigid contact lenses, but the most common problem with this approach is the mechanical and hypoxic complications caused by adherence of the lens edge to the peripheral cornea.[8,21,22] In the three-point contact approach, there are two more points of contact opposed at 180 degrees in addition to central contact, thus distributing the load from the center to other healthy areas of the cornea and providing maximum apex protection.[8,21,22] For this reason, the three-point contact approach is the most preferred. We also use this approach in clinical practice.

With HCLs, their soft skirt provides centration and comfort while the rigid central component provides a healthy optical surface like RGPCLs. Complications related to both the lens designs and low oxygen permeability were fairly common with the first-generation HCLs produced in the 1980s (Saturn II; Barnes Hind, Inc., CA, USA) and SoftPerm; SBH, Sunnyvale, CA, USA).[23,24,25] Separation of the lens at the fusion site was the most common complication with the first HCL.[26] Cohen et al.[27] reported three cases of *Acanthamoeba* keratitis (one requiring therapeutic keratoplasty) in SoftPerm HCL users. Corneal edema due to tight lens application was observed in keratoconus patients as a result of using HCLs with hydrogel polymer skirts.[28] Fortunately, the incidence of lens-related complications has decreased with current next-generation HCLs due to their stronger fusion zone, high oxygen permeability, silicone hydrogel skirt design, and different skirt curves for better fit.[11] Of the next-generation HCLs, the UltraHealth HCL has a reverse geometry design and two basic parameters, vault value and skirt curvature. The AirFlex HCL and EyeBrid HCL have the same characteristics and two basic parameters, the base curve and skirt curve.

In this study, we aimed to compare the topographic data and clinical results of the next-generation AirFlex HCL and Rose K2 RGPCL fitted to patients with moderate to advanced keratoconus in our center. We observed that the HCL and RGPCL provided similarly significant visual gains in patients with moderate to advanced keratoconus. Hassani et al.[29] and Carracedo et al.[12] showed in their studies comparing the ClearKone HCL and RGPCLs that the HCL provided greater visual gain than the RGPCL. Hashemi et al.[30] compared 20 keratoconus patients using an HCL and 20 using an RGPCL and found that both lenses provided similar visual gains, consistent with our study. Uçakhan and Yeşiltaş[31] conducted a study with 33 patients (47 eyes) with irregular astigmatism who discontinued RGPCL use (due to intolerance in 68% and RGPCL failure in 32%) and were fitted with the AirFlex or EyeBrid Silicone HCL. They reported a 92% success rate after a mean of 10 months of use and 72% of the patients continued to use the HCL. In their study, the mean visual acuity with the HCL was 0.05 logMAR. Consistently, this value was 0.08 in our study, despite all patients having moderate or advanced keratoconus. Kloeck et al.[32] evaluated 54 patients (102 eyes) treated with next-generation HCLs (SynergEyes KC and ClearKone) and found that HCLs were reliable and provided high visual gain for keratoconus patients, consistent with our study. However, the lens discontinuation rate was 37.8% in their study, the most common reason for which was that the lens was uncomfortable.[32] In our study, no patients had limbal vascularization, corneal edema, or keratitis related to the use of the AirFlex HCL. Other studies conducted with next-generation HCLs also demonstrated none of these complications, as in our study.[11,14,27] However, with HCLs containing a hydrogel polymer skirt, tight lens fitting may cause complications associated with corneal hypoxia due to limited tear exchange and insufficient corneal oxygenation.[28] Altay et al.[33] reported that after an average of 4 months of using the UltraHealth HCL with silicone hydrogel skirts after keratoplasty surgery, 18 of 20 patients continued to use the lens successfully and no graft-related complications (decompression, rejection, and infection) were observed. There are two studies in the literature investigating the effect of HCLs on corneal endothelial cells. Acar et al.[34] evaluated 24 keratoconus patients and detected no change in corneal endothelial cell count or polymorphism and polymegathism rates after 6 months of HCL use (ClearKone, SynergEyes Inc.). Similarly, Dikmetas et al.[35] evaluated 45 eyes of 45 advanced keratoconus patients using the EyeBrid or Airflex HCL for at least 6 months and reported no change in corneal endothelial cell count or polymorphism and polymegathism rates after 6 months of HCL use.

In our study, we compared the results obtained with the two lenses according to cone location and determined that visual acuity increased more significantly in patients with central cones compared to those with paracentral cones. The only study in the literature evaluating HCLs and RGPCLs in terms of cone location and morphology is that by Kloeck et al.[32] Consistent with our study, they demonstrated that cone location affected lens compliance, with lower treatment success in patients with more peripherally located cones.[31] Although the difference was not statistically significant in our study, we noted that the HCL provided a greater increase in visual acuity in patients

with paracentral cones compared to the RGPCL. This may be attributable to the fact that the HCL's soft skirt improves centration and has a wider effect area.

These lenses may be inadequate in conditions that exceed the landing zone of the HCL, such as advanced pellucid marginal degeneration and keratoglobus. Again, the disadvantages of these lenses are that a special applicator is needed, lens fitting can take longer than with other RGPCLs, and the lenses are costly and their use is limited to 6 months.

Study limitations

Limitations of this study include the need for a larger patient sample with longer follow-up, and the lack of a questionnaire evaluating the comfort of lens use.

Conclusion

In our study comparing an HCL and RGPCL in moderate and advanced keratoconus, we observed that they were similar in terms of clinical fitting difficulties and that the HCL provided as much visual gain as the RGPCL. In light of the topographic data, both lenses provided more visual gain in patients with central cones, while the HCL provided greater visual gain than the RGPCL in patients with paracentral cones. In conclusion, our results demonstrate that RGPCLs are practical and reliable lenses with high optical success and continue to be the first-line option among the currently available keratoconus lenses. With new technology that combines the positive properties of rigid and soft lens materials in a single lens, next-generation HCLs have now become almost competitive with RGPCLs. Nevertheless, for HCLs to continue to compete, studies including larger patient groups with longer follow-up and investigating the effects of HCLs on the cornea and ocular surface are needed.

Ethics

Ethics Committee Approval: This prospective study was conducted in the Cornea Unit of the Ankara Bilkent City Hospital Clinic of Ophthalmology and adhered to the principles of the Declaration of Helsinki. Ethics committee approval for the study was obtained from the Clinical Research Ethics Committee of the Ankara Yıldırım Beyazıt University Faculty of Medicine (number: 26379996/223, date: 12.09.2018).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.S., Y.Y.T., N.Ç., Concept: Ö.S., Y.Y.T., N.Y., Design: Y.Y.T., Ö.S., N.Y., Data Collection or Processing: Y.Y.T., Analysis or Interpretation: Y.Y.T., Ö.S., N.Ç., Literature Search: Y.Y.T., Ö.S., Writing: Y.Y.T., Ö.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Long-term Follow-up Results of Primary Canaliculitis Patients

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Abstract

Objectives: To evaluate the demographic characteristics, clinical presentation, microbiologic profile, and treatment results of patients with primary canaliculitis.

Materials and Methods: Patients diagnosed and treated for primary canaliculitis between May 2014 and May 2021 were analyzed retrospectively.

Results: There were 26 patients with primary canaliculitis, including 17 females (65.4%) and 9 males (34.6%) with a mean age of 50.6±16.4 years (range: 9-80 years). Canaliculitis affected the right eye in 11 patients, the left eye in 13 patients, and bilateral involvement was seen in 2 patients. Inferior canaliculus involvement was more frequent (73%). The most common complaint was epiphora (46.1%). Five patients (19.2%) were wrongly diagnosed as chronic conjunctivitis. The time interval between the beginning of symptoms and canaliculitis diagnosis was 18.2±14.3 months (range: 1-60 months). Canaliculotomy and curettage of canalicular content with dacryolith removal were performed in 23 patients. After surgery, antibiotic irrigation of the canaliculus was added to the treatment regimen in 12 of these 23 patients. Intracanalicular antibiotic therapy was administered to the remaining 3 patients. The most cultured organism was *Actinomyces* (6 patients). *Gemella* (1 patient), *Porphyrom*onas (1 patient), *Candida parapsilosis* (1 patient), *Citrobacter koser*i (1 patient) were also grown in culture. The follow-up time of patients was 26.2±23.7 months (range: 6-83 months). All symptoms and findings resolved in all patients in one month. In two patients, recurrence occurred at 4 and 16 months after surgical treatment. With appropriate treatment, no further recurrence was seen in either patient over 24-month follow-up. One patient presented with iatrogenic canaliculus blockage during follow-up.

Conclusion: Primary canaliculitis is often overlooked and can be misdiagnosed. The most common symptom was epiphora. All patients with epiphora and chronic conjunctivitis should be examined carefully for canaliculitis.

Keywords: Actinomyces, canaliculitis, canaliculotomy, conjunctivitis, curettage

Introduction

Primary canaliculitis is chronic inflammation of the proximal lacrimal pathway.[1] The most common signs and symptoms are epiphora, medial canthal swelling, punctal or canalicular edema, pouting punctum, lower eyelid erythema, concretions, and mucopurulent discharge. As the manifestations of canaliculitis are similar to other diseases of the lacrimal apparatus, in many cases the diagnosis is delayed or misdiagnosed as chronic conjunctivitis, chalazion, or dacryocystitis, resulting in inadequate or incorrect treatment.[2,3] Treatment with topical eye drops alone results in a high recurrence rate.[4] Surgical removal of concretions is considered imperative for a permanent cure, and the benefits over conservative treatment have been proven.[5]

The specific objective of this study was to evaluate the demographic characteristics, treatments, and long-term outcomes of patients with primary canaliculitis.

Materials and Methods

The medical records of patients diagnosed as having primary canaliculitis in the oculoplasty unit of our hospital between May 2014 and May 2021 were reviewed retrospectively. Ethics committee approval was obtained from the Ankara Bilkent City Hospital Clinical Research Ethics Committee (date of approval: 17/11/2021; protocol no: E1/2114/2021). The diagnosis of primary canaliculitis was based on clinical symptoms and signs.

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Data including patients' demographic characteristics, symptoms, symptom durations, previous clinical diagnoses, treatments, and long-term outcomes were collected. All patients were diagnosed based on clinical findings such as epiphora, punctal or canalicular edema, erythema (Figure 1), concretions (Figure 2), and purulent discharge from the punctum upon gentle pressure. Figure 2 shows one of our patients with sulfur granules.

Inclusion criteria were the presence of clinical findings suggesting typical canaliculitis and patent lacrimal syringing of the unaffected canaliculi. Exclusion criteria were cases of secondary canaliculitis due to foreign body in the punctum and canaliculus (e.g., eyelash, punctal plug) and obstruction of nasolacrimal duct drainage.

We applied two different treatment modalities. Intracanalicular antibiotic therapy was administered to patients who presented early (within 6 months) and had mild symptoms, patent lacrimal syringing through the unaffected canaliculi, dacryoliths, and purulent discharge from the punctum when mild pressure was applied. For patients who presented late (after 6 months; dacryoliths tend to be indurated in the late period), had recurrent canaliculitis, and/or were misdiagnosed underwent canaliculotomy and curettage of canalicular content with dacryolith removal. Depending on clinical severity, some patients received postoperative intracanalicular antibiotic treatment daily for the first week, then weekly for one month (Figure 3).

In intracanalicular antibiotic therapy without surgery, the canaliculus was irrigated with cefuroxime (750 mg/mL, 6 mL; Deva Holding, İstanbul, Türkiye) once a day for 5 days. A wide spectrum of topical antibiotics was given 8 times a day until the assessment of microbiologic culture results.

In surgical treatment, after local anesthesia, a Bowman lacrimal probe was passed into the affected canaliculus and an incision was made with a number 11 blade in the affected canaliculus. Canalicular curettage was performed using a chalazion curette. The canaliculi were irrigated with cefuroxime (750 mg/mL, 6 mL). The patients were treated with hot compresses and topical fluoroquinolone 8 times daily for 10 days. After canaliculotomy, intracanalicular cefuroxime was applied daily for the first week, then weekly for one month. The antibiotic regimen was refined according to culture results and sensitivities. No silicone intubation or reconstruction was performed.

Dacryoliths and purulent material obtained during surgery were sent to the microbiology laboratory for analysis using anaerobic transport medium. For patients who received only intracanalicular antibiotic therapy, mucopurulent material expressed from the affected canaliculus before antibiotic irrigation was sent to the microbiology laboratory. Direct Gram staining revealed gram-positive, branching filamentous structures. Cultures were performed to ascertain the presence of aerobic and anaerobic bacteria and fungi. Columbia agar was incubated at 37 °C in anaerobic conditions for 5 days. Blood agar and MacConkey agar plates were incubated at 37 °C for 24-48 hours. Sabouraud dextrose agar plates were incubated at both 25 °C and 37 °C.

Results

Of 26 patients who consented to treatment, 17 (65.4%) were female and 9 (34.6%) were male. The mean age was 50.6±16.4 years (range: 9-80 years). Canaliculitis affected the right eye in 11 patients, the left eye in 13 patients, and was bilateral in 2 patients. Inferior canalicular involvement was more frequent (73%). The most common complaint was epiphora (46.1%). Sixteen patients (61.5%) were misdiagnosed as having chronic conjunctivitis and treated previously. Two patients presented for unresolved epiphora after dacryocystorhinostomy. Other causes of hospital admission were purulent discharge, itching, redness, pain, and swelling of the canalicular area. The mean time from symptom onset to canaliculitis diagnosis was 18.2±14.3 months (range: 1-60 months). The demographic characteristics, treatment, and follow-up data of the patients are shown in Table 1.

Canaliculotomy and curettage of canalicular content with dacryolith removal were performed in 23 patients. After surgery, antibiotic irrigation of the canaliculus was added to the treatment

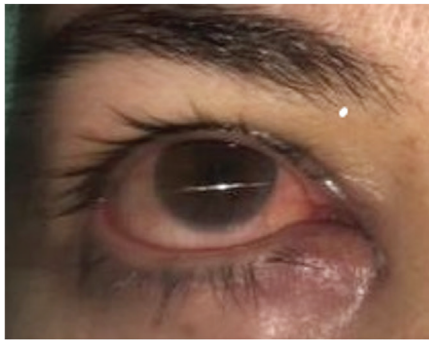

Figure 1. Clinical appearance of the right inferior punctum before treatment in a patient with primary canaliculitis. Hyperemia of the conjunctiva and edematous inferior canaliculus are evident

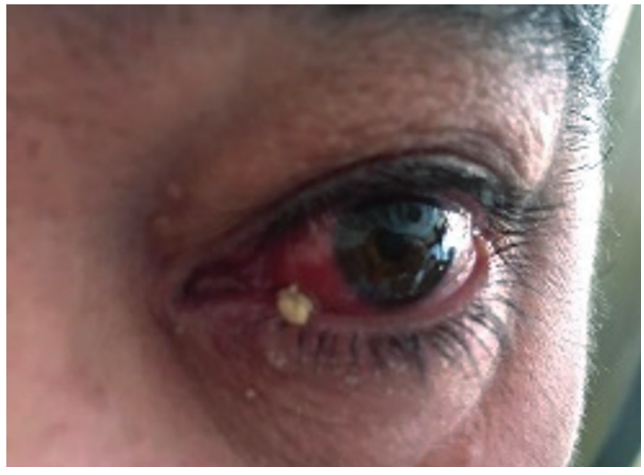

Figure 2. Typical sulfur granule appearance in canaliculitis

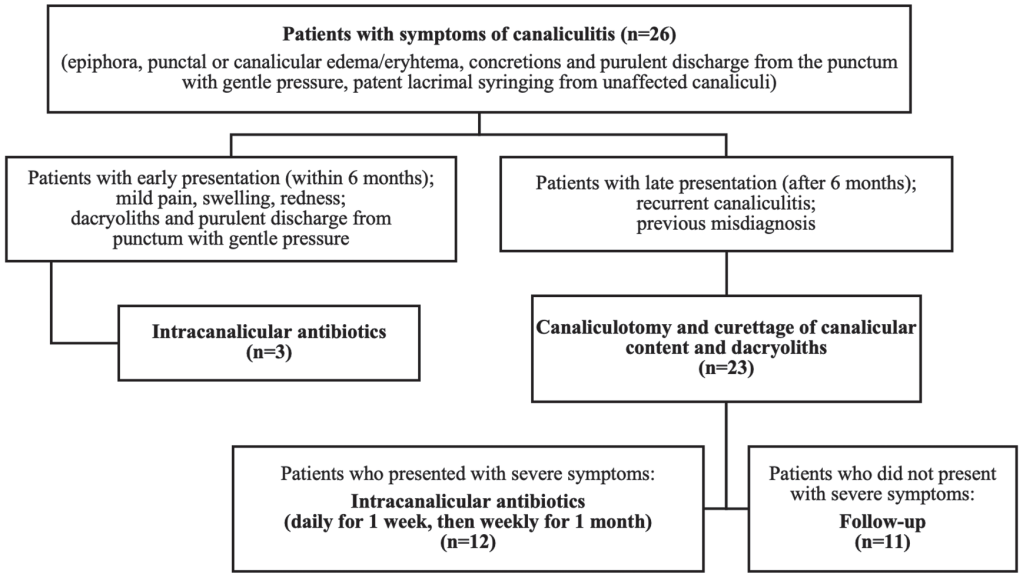

Figure 3. Treatment plan of canaliculitis

regimen in 12 of these 23 patients. The remaining 3 patients who did not undergo surgery received intracanalicular antibiotic therapy. All of these patients had been administered topical treatment with fluoroquinolone.

The most cultured organism was *Actinomyces* (6 patients). *Gemella* (1 patient), *Porphyromonas* (1 patient), *Candida parapsilosis* (1 patient), and *Citrobacter koseri* (1 patient) were also established in culture (Table 2). The mean follow-up time was 26.2±23.7 months (range: 6-83 months). Signs and symptoms resolved in all patients within 1 month. In 2 patients, recurrence occurred at 4 and 16 months after treatment. Canaliculotomy and curettage of canalicular content with dacryolith removal was performed in one of these patients, and intracanalicular antibiotic irrigation was done for the other. After appropriate treatment, no further recurrence was seen in either patient over 24-month follow-up. In 1 patient, iatrogenic canaliculus blockage was diagnosed during follow-up.

Table 1. Demographic, clinical, and follow-up data of primary canaliculitis patients

	Number (%)
Age (years)*	50.6±16.4 (9-80)
Gender	
Female	17 (65.4)
Male	9 (34.6)
Laterality	
Right	11 (42.3)
Left	13 (50.0)
Bilateral	2 (7.6)
Location	
Superior canaliculus	7 (26.9)
Inferior canaliculus	19 (73.1)
Mean time to diagnosis (months)	18.2±14.3
Follow-up time (months)*	26.2±23.7 (6-83)
Recurrence	2 (7.6)
Iatrogenic canaliculus blockage	1 (3.8)

*Data presented as mean ± standard deviation (range)

Table 2. Microbiological profile of primary canaliculitis patients

Etiologic agent	Number (%)
Actinomyces	6 (23)
Candida parapsilosis	1 (3.8)
Gemella	1 (3.8)
Citrobacter koseri	1 (3.8)
Porphyromonas	1 (3.8)

Discussion

The canaliculi are an important component of the lacrimal drainage system. They begin at the lacrimal puncta and mostly converge to form the common canaliculus. Canaliculitis is inflammation of the lacrimal canaliculus and accounts for only 2% to 4% of all patients with lacrimal pathology.[5] The condition may be misdiagnosed and treated as conjunctivitis, blepharitis, dacryocystitis, or chalazion, thus leading to prolonged morbidity.[5,6,7] The current study aimed to assess patients with primary canaliculitis and increase awareness of this rare and diagnostically challenging condition.

Canaliculitis is classified as either primary or secondary. While primary canaliculitis is usually caused by an infection, secondary canaliculitis is most commonly associated with punctal plug insertion for the treatment of dry eye, intracanalicular plug migration, or a foreign body in the punctum or canaliculus.[6,8] We only included patients with primary canaliculitis in this study.

Older women have a higher prevalence of canaliculitis in the literature.[9,10] In our study, females (65.4%) were more affected than males (34.6%) and the patients' mean age was 50.6±16.4 years (range: 9-80 years). Our findings are consistent with the literature.

The masking clinical manifestations of canaliculitis and low awareness among general ophthalmologists often lead to late diagnosis.[11] Sixteen of our 26 patients were previously misdiagnosed and treated for chronic conjunctivitis. The mean duration of symptoms prior to canaliculitis diagnosis in our study was 18.2±14.3 months (range: 1-60 months). This is longer than the intervals reported in two other studies by Kaliki et al.[13] and Kim et al.[14] For this reason, we think that increased awareness is needed to enable early diagnosis, and this condition should be considered when patients present with complaints of epiphora or recurrent conjunctivitis.

Dacryocystography and ultrasound biomicroscopy are widely used for the diagnosis of canaliculitis.[5] However, the use of a detailed diagnostic tool such as dacryocystography can lead to scar tissue because of iatrogenic trauma and is not absolutely necessary for diagnosis.[5] In the present study, all patients were diagnosed based on clinical manifestations (epiphora, punctal or canalicular edema, erythema, concretions, and purulent discharge expressed from the punctum with gentle pressure). We did not use dacryocystography or ultrasound biomicroscopy.

Canaliculitis can be misdiagnosed as dacryocystitis or nasolacrimal duct obstruction. Patent irrigation of the nasolacrimal duct through the unaffected canaliculus of the same eye is important in the differential diagnosis.[14]

The prevalence of inferior canaliculus involvement was higher (73%) in the present study compared to other studies.[11,12,15] To our knowledge, there is no explanation in the literature regarding which canaliculi are most affected and the reason for this. Our findings may be related to gravity and the anatomical structure of the inferior canaliculi. The lower canaliculi are almost entirely horizontal and taller than the upper canaliculi,[6] and gravity may predispose the lower canaliculi to bacterial accumulation. In contrast to our study, Kim et al.[14] reported that the upper and lower canaliculi were equally affected, while Vécsei et al.[16] reported that the upper canaliculus was more frequently involved. Most of the patients in our study had unilateral involvement (92%).

Treatment with only topical antibiotic drops, antibiotic irrigation of the canaliculi, or punctal curettage alone is associated with high recurrence rates. This is because antibiotics are unable to penetrate canalicular concretions.[5] Kaliki et al.[13] argued that 41% of patients who were managed without surgery required additional treatment. No additional treatment was needed by our patients treated with intracanalicular antibiotic irrigation. Their symptoms completely resolved. However, these patients needed to come to the hospital more often than patients treated with surgery. Concretions may prevent antibiotics from killing the bacteria and are therefore one of the main risk factors for recurrent canaliculitis.[15]

Curettage with or without one-snip punctoplasty and canaliculotomy are the recommended approaches to the surgical treatment of primary canaliculitis.[2,5,13,16,17,18,19] Canalicular dilation can occur in association with canaliculitis and may lead to canalicular stasis and bacterial propagation.[17] Canalicular dilation was seen in one patient in our study. Yuksel et al.[17] demonstrated that in cases without serious dilation, punctotomy/canaliculotomy and curettage may be sufficient for treatment. Canaliculotomy provides a higher success rate, but scarring and dysfunction of the lacrimal pump may occur. Canaliculoplasty with lacrimal intubation may be essential for a definitive cure in cases with canalicular dilations. This technique prevents iatrogenic canalicular scarring and preserves lacrimal pump function. Canaliculoplasty may have an important role in the prevention of canalicular stasis. Additionally, one-snip punctoplasty was found to be efficacious in cases without significant canalicular dilation.[17]

In the literature, there is one study that compared anatomical and functional success rates between patients with and without silicone tube intubation.[2] Wang et al.[2] reported that canaliculotomy with silicone tube intubation showed better outcomes, with significantly higher anatomical (100% vs. 73.8%) and functional success rates (87.5% vs. 60.9%) than in the group without silicone tube intubation. However, complete resolution of canalicular edema, erythema, and purulent discharge was seen in all patients postoperatively, and no recurrent infections were observed in any of the patients during follow-up.[2] Su et al.[1] observed complete resolution in 78.6% of patients after canaliculotomy with stent placement. In contrast, in another study complete resolution was achieved in 97.2% of the patients after canaliculotomy and curettage without stent intubation.[15] In the current study, no stent placement was performed and complete remission was achieved in 92% of the patients with a mean follow-up time of 26.2±23.7 months. Unfortunately, performing canaliculotomy with stent intubation was not an option because of the higher cost of stents in our hospital. Nevertheless, our results clearly demonstrate that canaliculotomy without stent intubation may be a good choice for these patients.

In our study, only one patient had canaliculus obstruction at follow-up, while the other patients had good canalicular function. We achieved a high functional success rate using canaliculotomy and curettage of canalicular content with dacryolith removal.

Canaliculitis severity and symptom duration are important criteria guiding our treatment approach. We applied intracanalicular antibiotics to patients with early presentation (within 6 months) and mild symptoms (3 patients). However, antibiotic irrigation is not appropriate for patients with accumulated stones in the canaliculi and severe symptoms. In these patients, we performed canaliculotomy and curettage of canalicular content with dacryolith removal. This surgical procedure was performed for 23 of our 26 patients. After surgery, antibiotic irrigation of the involved canaliculus was added to the treatment regimen if the patients had severe symptoms, recurrent canaliculitis, and presence of concretions (Figure 3).

In the literature, success rates in the conservative treatment of primary canaliculitis vary between 0% and 34.7%, while 80-100% recovery is reported after canaliculotomy.[5,16,18,19] In our study, complete resolution of primary canaliculitis was noted in 100% of our patients in long-term postoperative follow-up. Two patients had recurrence 4 and 16 months after treatment. Canaliculotomy and curettage of canalicular content with dacryolith removal was repeated in one of the patients, and intracanalicular antibiotic irrigation was performed for the other patient. No further recurrence was seen in either patient in 24 months of follow-up.

Conventionally, the causative pathogen of canaliculitis is reported to be *Actinomyces israelii*, an anaerobic gram-positive bacillus. It is associated with chronic purulent granulomatous infection with typical sulfur granules.[20] Most recently, studies have shown an increased incidence of *Staphylococcus* and *Streptococcus* species.[5,9,11,13] Many other uncommon organisms like *Eikenella*, *Lactococcus*, *Nocardia*, and fungi also have been isolated from patients with canaliculitis.[6] Concretions were initially considered pathognomonic of *Actinomyces*, but many other organisms have also been associated with concretions in other studies.[11,13,15,21] In the present study, discharge and/or concretions from all patients were sent to the microbiology laboratory for evaluation and microbiological cultures were positive in only 10 patients (38%). *Actinomyces israelii* was most frequently isolated organism in the current study (23%), and other cultured organisms included *Gemella*, *Porphyromonas*, *Candida parapsilosis*, and *Citrobacter koseri*.

This study reflects the long-term results of a tertiary ophthalmology center to which patients were referred from many different centers in our country. However, the main limitation is its retrospective design. Another limitation is that we could not make a comparison between patients who received only intracanalicular antibiotic therapy and those who underwent surgery, because the number of patients who received early treatment was small. However, this led us to believe that diagnosis is usually delayed in these patients, so we need to raise our awareness of early diagnosis.

Conclusion

Canaliculitis is an uncommon lacrimal pathway disease that can be overlooked and misdiagnosed for long periods. As a result, the appropriate treatment is generally delayed. The most common symptom in our patients was epiphora. All patients with epiphora and chronic conjunctivitis should be examined carefully for canaliculitis. The recommended treatment is canaliculotomy and curettage of canalicular content with dacryolith removal. In spite of appropriate treatment, the possibility of recurrence should always be kept in mind.

Ethics

Ethics Committee Approval: Ankara Bilkent City Hospital Clinical Research Ethics Committee (date of approval: 17/11/2021; protocol no: E1/2114/2021).

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: E.M.Ş., F.Ç.E., K.S.C., Concept: E.G.B., E.M.Ş., Design: E.M.Ş., Data Collection or Processing: E.G.B., E.M.Ş., K.S.C., F.Ç.E., E.E., Analysis or Interpretation: E.G.B., E.M.Ş., Literature Search: E.G.B., E.M.Ş., Writing: E.G.B., E.M.Ş., K.S.C., F.Ç.E.

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Original Article

Macular and Peripapillary Vascular Densities in Non-Glaucomatous Eyes of Patients with Unilateral Glaucoma

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Abstract

Objectives: Our purpose was to investigate vascular alterations in the non-glaucomatous eyes of patients with unilateral primary open angle glaucoma using optical coherence tomography angiography and to evaluate the role of vascular damage in glaucoma pathogenesis.

Materials and Methods: This cross-sectional study included 60 eyes of 30 patients with unilateral glaucoma (63.4±8.8 years) and 30 eyes of 30 healthy subjects (65.6±9.1 years). Three groups were formed: group A, affected eyes of unilateral glaucoma patients; Group B, non-glaucomatous eyes of unilateral glaucoma patients; and group C, healthy controls.

Results: When group A was compared with groups B and C, significant differences were detected in rim area, cup volume, mean cup/disc ratio, and retinal nerve fiber layer thickness parameters ($p<0.001$ for all). No significant difference was detected between groups B and C ($p>0.05$ for all). In peripapillary and macular vessel density (VD) comparisons, all parameters except intradisc VD were found to be lower in group A ($p<0.0167$ for all). No statistically significant difference was detected between groups B and C ($p>0.05$ for all).

Conclusion: The VD values in eyes with glaucoma were found to be lower than in the other two groups. However, no difference was observed between the non-glaucomatous eyes of glaucoma patients and those of healthy individuals. Thus, the results did not support our hypothesis that VD alterations would be observed in the fellow eyes of patients with unilateral glaucoma if the vascular pathway were responsible in the pathogenesis of glaucoma.

Keywords: Primary open-angle glaucoma, optical coherence tomography angiography, vascular density

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Introduction

In the pathogenesis of glaucoma, it is thought that damage occurs through mechanical, immunological, and vascular pathways.[1,2,3] The vascular pathway theory has become very popular in recent years.[4,5] Vascular dysfunction in the optic nerve head (ONH) and peripapillary retina is believed to be important in the pathogenesis of primary open-angle glaucoma (POAG).[6,7]

Optical coherence tomography angiography (OCTA) is a non-invasive angiography device that does not require a fluorescent substance.[8] The use of OCTA has become common in both the diagnosis and follow-up of glaucoma in recent years.[9]

Our hypothesis was that detecting vascular insufficiency in the peripapillary or macular area in the unaffected (and presumed intact) eyes of patients with unilateral glaucoma would support the vascular pathway theory of glaucoma pathogenesis. Therefore, in this study we investigated vascular changes in the unaffected eyes of patients with unilateral POAG using OCTA. The relationships between vessel density (VD) values and both structural and functional tests were also evaluated.

Materials and Methods

This cross-sectional study was conducted in Başkent University Hospital by analyzing the information of patients who presented between January 2018 and April 2019. The ethics committee of our university approved the project (no. KA19/59), and the research was carried out in accordance with the principles of the Helsinki Declaration. Written informed consent to participate in this research was obtained from all subjects.

The study included 60 eyes of 30 patients with unilateral POAG and 30 eyes of 30 healthy individuals. Best corrected visual acuity, spherical equivalent (SE), intraocular pressure

(IOP), and biomicroscopic anterior segment, dilated fundus, and gonioscopic examination findings were recorded. Peripapillary and macular OCT and OCTA were performed.

Patients who had undergone surgery except uncomplicated cataract surgery; had cataracts, vitreous opacity, or corneal cloudiness; had an SE greater than +/-6 diopters (D); had a history of any retinal pathology that may affect the accuracy of measurements; or had exfoliation syndrome and other causes of secondary open-angle glaucoma were excluded. As pseudoexfoliation glaucoma is generally asymmetric, all patients were examined by slit-lamp biomicroscopy after pupil dilation to avoid any misdiagnosis. All included patients had high IOP before treatment; normotensive patients were excluded. Subjects who had systemic disorders that could interfere with OCT and OCTA results were also excluded.

The inclusion criteria for the POAG group were as follows: an open angle in gonioscopy, glaucomatous optic nerve damage in both clinical examination and OCT, and a glaucomatous visual field (VF) defect confirmed on two consecutive reliable tests (fixation loss rate ≤20%, false-positive and false-negative error rates ≤25%). Glaucomatous VF defect was defined as a VF change fulfilling two or more of the following criteria: 1) outside the normal limits on the Glaucoma Hemifield Test, 2) three abnormal points with a probability of being normal of p<5% and one with p<1% by pattern deviation, or 3) a pattern standard deviation (PSD) of p<5%. In addition, the unaffected contralateral eye had to have an IOP <21 mmHg, open angle on gonioscopy, normal-appearing optic disc, and normal VF. The OCT disc, retinal nerve fiber layer thickness (RNFLT) and ganglion cell analysis (GCA) findings of these unaffected eyes were compatible with the patients' ages. The age-matched control group also had an open angle on gonioscopy, IOP <21 mmHg, normal-appearing optic disc, and normal OCT disc, RNFLT, GCA, and VF. The affected eyes of unilateral glaucoma patients were defined as group A, their unaffected eyes as group B, and the healthy control group eyes as group C.

OCTA images were obtained using the RTVue XR Avanti (Optovue; version 2017.1.0.151, Fremont, CA, USA) device, which can scan 70,000 A-mode images per second using 840 nm wavelength light. Retinal vascular structures in the scanned area were segmented automatically by the AngioVue software. Patients with signal strength above 6/10 were included.

Disc OCTA measurements were performed using 2 mm and 4 mm diameter rings based on the disc center. A 4.5x4.5 mm area comprised the whole image area. The area within the 2 mm ring is defined as the intrapapillary region and the area between the 2 mm and 4 mm rings as the peripapillary area. For the determination of the radial peripapillary capillary (RPC) network, the software automatically divides the measurement area into four layers. RPC measurements are determined by the density measurements of the region between the internal limiting membrane (ILM) and the lower limit of the retinal nerve fiber layer (RNFL). Capillary densities were used to evaluate the vascular network of the RNFL.

To evaluate the superficial plexus responsible for supplying the ganglion cell layer in a 6x6 mm area in macular OCTA measurements, a layer with an upper limit of the ILM and lower limit 10 µm below the inner plexiform layer was automatically created. Anatomical structures were defined by three concentric rings centered on the fovea. The innermost 1 mm diameter circle represents the fovea, the annulus between the middle 3 mm diameter ring and the innermost 1 mm ring represents the parafovea, and the annulus between the outermost 6 mm diameter ring and the middle 3 mm diameter ring represents the perifovea. A 6x6 mm area comprises the whole image area.

Optic nerve cup-to-disc ratio, rim area, and disc area values, RNFLT values, and GCA measurements consisting of minimum and mean ganglion cell layer and inner plexiform layer (GCL + IPL) thickness values were obtained automatically by a Cirrus HD spectral domain OCT device (Carl Zeiss Meditec, Dublin, CA, USA). Patients with a signal strength ≥6/10 were included.

Patients who had a 24-2 visual interactive measurement (24-2 Swedish interactive thresholding algorithm) with a Humphrey automated VF device (Humphrey Field Analyzer II 750) were included. Mean deviation (MD) and PSD values were recorded.

IOP measurements were made by two glaucoma specialists (S.G.G. and Ü.E.) between 8:30 and 10:30 a.m. with a Goldmann applanation tonometer mounted on a slit lamp (Takagi slit lamp microscope SM-70N, Takagi Inc., Manchester, UK) with fluorescein under topical anesthesia.

Statistical Analysis

IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY) was used for the analysis. Descriptive statistics were used to summarize the data. Analytical evaluations were made to compare the groups. In the hypothesis tests, Pearson chi-square test was used to compare qualitative variables, Mann-Whitney U test was used to compare continuous quantitative variables between independent groups, and the Kruskal-Wallis analysis of variance (H test) was used to compare continuous quantitative variables among more than two groups. For variables that had significant differences between groups, a Bonferroni-adjusted Mann-Whitney U test was performed with adjusted alpha value taken as 0.0167. A Spearman's rank correlation test was used to investigate the correlation between VD and structural and VF parameters. The data were checked for normal distribution by Kolmogorov-Smirnov test. P<0.05 was considered significant.

Results

Both eyes of 30 patients with unilateral POAG were included. Demographic and clinical features are given in Table 1. The groups were similar in age, gender, lens status, visual acuity, IOP, and SE (p>0.05). In group A, 10 patients followed a drug regimen with one active substance, 11 patients with two active substances, 6 patients with three active substances, and 3 patients with four active substances. All patients' IOP values were below 21 mmHg with treatment.

The mean MD and PSD values in group A were -7.64±6.33 decibels (dB) and 6.17±3.95 dB, respectively. These values were significantly different than those in groups B and C (p<0.001 for all) (Table 1). Groups B and C had similar values for both parameters (p=0.99 and p=0.98, respectively).

The values obtained by OCT are shown in Table 2. Except for disc area, all optic disc parameters, RNFLT, and mean and minimum GCL + IPL thickness values differed significantly in group A compared to both group B and group C (p<0.001 for all values except disc area). No significant difference was found between groups B and C (p>0.05).

Peripapillary and macular VD measurements of the groups are presented in Table 3. All parameters except inside disc vessel density (IDVD) were found to be significantly higher in groups B and C than in group A (p<0.0167 for all), but there was no statistically significant difference between groups B and C (p>0.05).

Correlations between OCT and VD values are examined in Table 4. Mean RNFLT correlated with peripapillary VD (PPVD) values in all three groups, while mean whole image PPVD (WI-PPVD) measurements showed significant correlation with RNFLT in groups A and B. In all groups, both mean and minimum GCL + IPL thickness correlated with PPVD and WI-PPVD values.

Whole image macular VD (WI-MVD) values showed significant correlation with mean RNFLT and mean GCL + IPL thickness values only in group A (p=0.02, r=0.42 and p=0.007, r=0.48, respectively). Minimum GCL + IPL thickness and WI-MVD values were correlated in groups A and B (p=0.04, r=0.37 and p=0.03, r=0.38, respectively) (Table 4).

Table 5 shows correlations between VF values and mean RNFLT, mean GCL + IPL thickness, WI-PPVD, PPVD, WI-MVD, and parafoveal VD (PFVD) values in groups A and B. In group A, MD values were correlated with all parameters (p<0.05) except mean RNFLT. Similarly, PSD negatively correlated with all parameters in group A (p<0.05).

Table 1. Demographic structures and clinical features of the groups

	Group A	Group B	Group C	*p* ‡	*p1*	*p2*	*p3*
Age (years) *	63.4±8.8	63.4±8.8	65.6±9.1		-	0.35	-
Gender (n women/men)†	17/13	17/13	18/12		-	0.87	-
Lens status (n pseudophakic/phakic)†	12/18	7/23	13/17		0.35	0.22	0.45
Spherical equivalent (diopters)	-0.6±1.6	-0.6±1.51	-0.13±1.5	0.35	-	-	-
Visual acuity (Snellen)	0.84±0.22	0.92±0.12	0.91±0.10	0.37	-	-	-
Intraocular pressure (mmHg)	18.03±5.39	15.6±3.11	17.03±2.53	0.07	-	-	-
Mean deviation (dB)	-7.64±6.33	-0.90±0.83	-0.76±0.64	**<0.001**	**<0.001**§	**<0.001**§	**0.99**§
Pattern standard deviation (dB)	6.17±3.95	2.05±1.06	1.94±0.72	**<0.001**	**<0.001**§	**<0.001**§	**0.98**§

*Mann-Whitney U test, †Pearson chi-square test, ‡Kruskal-Wallis H test, §Bonferroni-adjusted Mann-Whitney U test; *p1*: Group A vs. group B, *p2*: Group A vs. group C, *p3*: Group B vs. group C

Table 2. Retinal nerve fiber layer thickness and ganglion cell analysis of the groups

	Group A	Group B	Group C	*p*	*p1*	*p2*	*p3*
Rim area (mm²)	0.90±0.23	1.22±0.16	1.29±0.24	**<0.001**	**<0.001**	**<0.001**	0.47
Disc area (mm²)	2.39±0.34	1.77±0.27	1.75±0.25	**0.67**	-	-	-
Cup volume (mm³)	0.31±0.21	0.14±0.1	0.14±0.16	**<0.001**	**<0.001**	**<0.001**	0.31
Mean cup/disc ratio	0.68±0.11	0.53±0.11	0.46±0.17	**<0.001**	**<0.001**	**<0.001**	0.13
Vertical cup/disc ratio	0.69±0.12	0.49±0.11	0.45±0.16	**<0.001**	**<0.001**	**<0.001**	0.70
Mean RNFLT (µm)	70.1±11.57	90.4±7.08	91.43±8.71	**<0.001**	**<0.001**	**<0.001**	0.59
Inferior RNFLT (µm)	83.50±23.05	115.80±11.7	116.66±13.65	**<0.001**	**<0.001**	**<0.001**	0.63
Nasal RNFLT (µm)	61.90±10.9	69.40±10.33	70.56±11.03	**<0.001**	**<0.001**	**<0.001**	0.76
Superior RNFLT (µm)	69.80±17.36	74.26±8.67	111.73±15.19	**<0.001**	**<0.001**	**<0.001**	0.98
Temporal RNFLT (µm)	55.50±11.95	70.90±13.8	66.70±9.91	**<0.001**	**<0.001**	**<0.001**	0.41
Minimum GCL + IPL (µm)	59.36±10.5	77.20±6.37	78.20±4.95	**<0.001**	**<0.001**	**<0.001**	0.65
Mean GCL + IPL (µm)	67.80±8.39	79.50±6.40	80.40±4.79	**<0.001**	**<0.001**	**<0.001**	0.59

RNFLT: Retinal nerve fiber layer thickness, GCL + IPL: Ganglion cell layer+internal plexiform layer thickness. *P*: Kruskal-Wallis H test, *p1*: Group A vs. group B, *p2*: Group A vs. group C, *p3*: Group B vs. group C (Bonferroni-adjusted Mann-Whitney U test)

Table 3. Peripapillary and macular vessel density measurements of the groups

	Group A	Group B	Group C	*p*	*p1*	*p2*	*p3*
WI-PPVD	39.73±5.91	48.42±3.71	48.82±2.52	**<0.001**	**<0.001**	**<0.001**	0.94
PPVD	40.97±7.33	51.4±3.92	51.06±3.05	**<0.001**	**<0.001**	**<0.001**	0.89
IDVD	43.67±6.52	46.38±6	45.88±5.27	**0.13**	-	-	-
SH-PPVD	41.06±7.5	47.70±8.8	51.67±3.11	**<0.001**	**<0.001**	**<0.001**	0.68
IH-PPVD	41.07±8.7	51.50±4.0	51.62±3.26	**<0.001**	**<0.001**	**<0.001**	0.76
I-PPVD	43.60±10.79	52.26±5.29	53.96±3.68	**<0.001**	**<0.001**	**<0.001**	0.15
N-PPVD	39.20±9.35	53.3±7.83	50.86±5.19	**<0.001**	**<0.001**	**<0.001**	0.15
S-PPVD	38.83±10.85	50.80±5.18	51.60±4.28	**<0.001**	**<0.001**	**<0.001**	0.62
T-PPVD	42.80±9.8	50.96±5.56	51.16±7.08	**<0.001**	**0.002**	**<0.001**	0.35
WI-MVD	40.10±4.79	46.12±4.62	47.27±3.49	**<0.001**	**<0.001**	**<0.001**	0.51
PFVD	42.11±5.84	47.59±6.60	48.75±4.58	**<0.001**	**0.001**	**<0.001**	0.62
SH-PFVD	42.13±6.56	47.32±7.13	51.67±3.11	**<0.001**	**0.003**	**<0.001**	0.69
IH-PFVD	42.09±5.55	47.92±6.33	51.65±3.26	**<0.001**	**<0.001**	**<0.001**	0.56
I-PFVD	42.93±5.57	48.05±7.34	49.44±5.64	**<0.001**	**0.002**	**<0.001**	0.55
N-PFVD	41.84±6.13	45.66±10.6	47.83±5.52	**<0.001**	**0.005**	**<0.001**	0.80
S-PFVD	42.46±7.45	47.67±7.3	48.81±5.78	**<0.001**	**0.009**	**0.001**	0.54
T-PFVD	41.09±7.32	47.67±6.37	48.90±4.40	**<0.001**	**<0.001**	**<0.001**	0.38

PPVD: Peripapillary vessel density, IDVD: Intradisc vessel density, PFVD: Parafoveal vessel density, MVD: Macular vessel density, WI: Whole image, SH: Superior hemisphere, IH: Inferior hemisphere, S: Superior quadrant, T: Temporal quadrant, I: Inferior quadrant, N: Nasal quadrant. *P*: Kruskal-Wallis H test, *p1*: Group A vs. group B, *p2*: Group A vs. group C, *p3*: Group B vs. group C (Bonferroni-adjusted Mann-Whitney U test)

Discussion

In this study we investigated the peripapillary and macular VDs in patients with unilateral POAG and healthy individuals. VD in POAG has been investigated in the literature before. Toshev et al.[10] observed lower PPVD values in POAG than in ocular hypertension. Similarly, Nascimento et al.[11] found that POAG patients had lower PPVD than healthy controls. In our study, we observed that PPVD values in eyes with glaucoma were lower than in fellow unaffected eyes and the control group, except for IDVD. Yip et al.[12] found that macular VDs decreased with PPVD in glaucoma, and that PPVD was superior in distinguishing healthy and glaucomatous eyes. Triolo et al.[13] compared healthy individuals to those with glaucoma or suspected glaucoma and found a decrease in PPVD but not in macular VD. In our study, we observed that all macular VDs were lower in glaucomatous eyes than in fellow unaffected eyes and the control group. No significant difference was observed in any macular VD or PPVD parameters between the fellow unaffected eyes of the patients and the control group. Therefore, there were no data supporting our hypothesis that there is a vascular predisposition in the pathogenesis of POAG.

In a study investigating the effect of optic disc perfusion and VD on glaucoma progression, Wang et al.[1] found that PPVD and RNFLT values showed high correlation. Chung et al.[14] also found PPVD and RNFLT values to be correlated and showed that the diagnostic ability of VD in glaucoma was similar to that of RNFLT measurements. In our study, the mean RNFLT and PPVD values were correlated in all three groups, as were GCA parameters and PPVDs. Wang et al.[1] found a high correlation between PPVD and ganglion cell complex (GCC) measurements and reported that GCA showed a much stronger relationship with optic disc perfusion and VDs than other structural tests.

In our study, a correlation between mean RNFLT and WI-MVD values was only observed in group A. When GCA values were analyzed with macular VDs, a correlation was only found between mean GCL + IPL thickness and WI-MVD in group A. In group A and group B, a weak correlation was found between minimum GCL + IPL thickness and WI-MVD. Triolo et al.[13] did not find a correlation between GCC and macular VDs in their study of glaucoma patients.

In light of the information we obtained, we think that PPVD values are superior to macular VD values for glaucoma diagnosis and follow-up. WI-PPVD and PPVD values especially are correlated with RNFLT and GCA values. We believe that PPVD measurements may be important in the early diagnosis and treatment follow-up of glaucoma.

Poli et al.[15] investigated the correlation of peripapillary and macular VDs with GCC thickness, RNFLT values, and VF indices and found the highest correlation with PPVD. Chen et al.[16] found that VF values showed the highest correlation with WI-PPVD, followed by PPVD. They also concluded that macular VD values showed lower correlation with VF parameters than GCC thickness and RNFLT. Wang et al.[1] also obtained similar results, and found that optic disc perfusion parameters and VDs showed higher correlations with MD, RNFLT, and GCC thickness values. In our study, WI-MVD, PFVD, WI-PPVD,

Table 4. Correlation analysis of vessel density values and optical coherence tomography parameters in all groups

		Group A	Group B	Group C
Mean RNFLT vs. WI-PPVD	*p*	**0.002**	**0.02**	0.11
	r	**0.54**	**0.44**	0.30
Mean RNFLT vs. PPVD	*p*	**0.005**	**0.03**	**0.04**
	r	**0.50**	**0.40**	**0.38**
Mean GCL + IPL vs. WI-PPVD	*p*	**0.001**	**0.01**	**0.02**
	r	**0.58**	**0.46**	**0.43**
Mean GCL + IPL vs. PPVD	*p*	**0.002**	**0.001**	**0.001**
	r	**0.54**	**0.57**	**0.56**
Minimum GCL + IPL vs. WI-PPVD	*p*	**0.004**	**0.01**	**0.05**
	r	**0.51**	**0.45**	**0.37**
Minimum GCL+IPL vs. PPVD	*p*	**0.005**	**0.001**	**0.02**
	r	**0.50**	**0.58**	**0.42**
Mean RNFLT vs. WI-MVD	*p*	**0.02**	0.77	0.26
	r	**0.42**	0.06	0.21
Mean RNFLT vs. PFVD	*p*	0.48	0.98	0.23
	r	0.14	0.006	0.23
Mean GCL + IPL vs. WI-MVD	*p*	**0.007**	0.05	0.16
	r	**0.48**	0.36	0.26
Mean GCL + IPL vs. PFVD	*p*	0.14	0.21	0.44
	r	0.28	0.24	0.15
Minimum GCL + IPL vs. WI-MVD	*p*	**0.04**	**0.04**	0.08
	r	**0.37**	**0.38**	0.33
Minimum GCL + IPL vs. PFVD	*p*	0.17	0.13	0.22
	r	0.26	0.28	0.23

RNFLT: Retinal nerve fiber layer thickness, PPVD: Peripapillary vessel density, WI: Whole image, GCL + IPL: Ganglion cell layer + internal plexiform layer, MVD: Macular vessel density, PFVD: Parafoveal vessel density. Spearman's rank correlation coefficient test was used. *p*: Statistical significance of correlation coefficient, *r*: Spearman's correlation coefficient

Table 5. Correlation of peripapillary vessel density, parafoveal vessel density, retinal nerve fiber layer thickness, and ganglion cell analysis measurements with visual field MD-PSD values

		Group A	Group B
WI-PPVD vs. MD	*p*	**<0.001**	0.15
	r	**0.69**	0.27
PPVD vs. MD	*p*	**<0.001**	0.19
	r	**0.61**	0.25
WI-MVD vs. MD	*p*	**0.001**	0.52
	r	**0.56**	0.12
PFVD vs. MD	*p*	**0.001**	0.97
	r	**0.59**	-0.008
Mean RNFLT vs. MD	*p*	0.05	0.08
	r	0.36	0.33
Mean GCL + IPL vs. MD	*p*	**0.03**	0.16
	r	**0.36**	0.27
WI-PPVD vs. PSD	*p*	**<0.001**	0.20
	r	**-0.74**	-0.24
PPVD vs. PSD	*p*	**<0.001**	0.80
	r	**-0.62**	-0.05
WI-MVD vs. PSD	*p*	**0.004**	0.92
	r	**-0.51**	-0.02
PFVD vs. PSD	*p*	**0.03**	0.62
	r	**-0.41**	0.09
Mean RNFLT vs. PSD	*p*	**0.02**	0.14
	r	**-0.42**	-0.28
Mean GCL + IPL vs. PSD	*p*	**0.026**	0.74
	r	**-0.41**	-0.05

PPVD: Peripapillary vessel density, WI: Whole image, MD: Mean deviation, MVD: Macular vessel density, PFVD: Parafoveal vessel density, RNFLT: Retinal nerve fiber layer thickness, GCL + IPL: Ganglion cell layer + internal plexiform layer, PSD: Pattern standard deviation. Spearman's rank correlation coefficient test was used. *p*: Statistical significance of correlation coefficient, *r*: Spearman's correlation coefficient

and PPVD values were correlated with both MD and PSD values in eyes with glaucoma, similar to the literature. The correlation of RNFLT and GCA values with MD and PSD values were examined along with VDs, and the strongest correlations for both MD and PSD were with WI-PPVD, followed by PPVD.

One of the interesting results of our study is that although IDVD was found to be lower in eyes with glaucoma, it did not differ statistically from healthy eyes like other parameters. As previously noted, the crowding of large vessels and the narrowness of the scanned area may have hindered accurate assessment of the superficial disc microcirculation.[17] In the study by Chung et al.,[14] VDs in the ONH, peripapillary, and macular regions in glaucomatous eyes were found to be significantly lower than those in healthy eyes. The authors stated that the VD parameters, with the exception of IDVD, were significantly correlated with OCT parameters and VF indices. IDVD again showed poor diagnostic ability.[14] Nascimento et al.[11] found that superficial ONH VD did not differ between glaucoma patients and healthy subjects, but POAG eyes showed a significantly lower VD in the deep ONH. In our study, IDVD was measured in the superficial layer where the RPC network was examined. Studies have shown that the posterior lamina cribrosa is the primary damaged area and the central area of the lamina cribrosa was more vulnerable to reduced blood supply following IOP elevation in glaucoma.[18,19] However, there are studies that have found a decrease in superficial ONH VD in eyes with glaucoma.[20,21] These differing results may be caused by differences in the determination of the superficial layer, whether the great vessels are excluded or not, and the use of different OCTA devices and processing algorithms.

Mangouritsas et al.[17] recently showed a significantly lower mean PPVD and WI-PPVD in eyes with unilateral preperimetric glaucoma compared with normal fellow eyes and reported that

mean PPVD and WI-PPVD were not significantly higher in healthy controls than in fellow eyes. The results of this study are consistent with ours. Structural tests of fellow eyes were also normal, as in our study. We consider this evidence that in glaucoma, vascular findings do not appear much earlier than structural tests can identify. In the future, prospective studies could investigate the transformation of unilateral patients over time into bilateral glaucoma to provide a better understanding of whether the vascular pathway has an effect on the development of POAG.

Yarmohammadi et al.[22] conducted a study to characterize VD in POAG patients with unilateral VF loss. They observed that mean RNFLT, GCC thickness, and rim area measurements in the unaffected eyes of POAG patients were higher than in their affected fellow eyes and lower than in healthy eyes. The unaffected eyes of POAG patients also showed lower VD in both the peripapillary and macular regions compared to healthy eyes. However, the method of this study was slightly different from our study. Patients had a glaucomatous VF defect in one eye and normal VF in the other eye, and the appearance of the optic disc was not considered in the determination of eligibility for patients in the POAG group. The lower VD in perimetrically unaffected fellow eyes in their study suggests that OCTA can detect microvascular changes in eyes at high risk of developing glaucoma before there is detectable VF damage. Our study included patients with unilateral POAG to determine whether vascular changes started before structural changes and whether POAG patients had a vascular predisposition. The unaffected eyes of the POAG patients in our study had normal optic disc appearance and their peripapillary and macular structural tests were consistent with their age. Thus, the unaffected eyes in our study were perimetrically and structurally normal. This methodological difference was a notable variance between the two studies in comparing unaffected eyes with healthy eyes.

Study Limitations

The low number of patients can be considered a limitation in this study. However, it should be remembered that POAG is often bilateral. Unilaterality is rare, and patients with additional diseases that may affect OCTA were excluded from the study.

In addition, the IOP values of the glaucomatous eyes of the patients included in the study were under control with antiglaucomatous therapy. The use of antiglaucomatous drops by the patients is another limiting factor of this study. However, the IOP values of the eyes in all groups were below 21 mmHg, thereby minimizing the effect of IOP on the vasculature.

Conclusion

In our study, microvascular changes were not observed in the unaffected eyes of individuals with unilateral glaucoma. In other words, there was no evidence supporting the presence of a vascular predisposition in the pathogenesis of POAG. However, a definite judgement can only be reached through prospective follow-up of these eyes. To gain a better understanding of the vascular pathogenesis of glaucoma, we believe observing changes in the vascular structures in eyes which are developing glaucoma during follow-up visits would be a suitable approach. In our study, VDs were correlated with structural and functional glaucoma examinations, and a high correlation with PPVDs in glaucomatous eyes was observed. Monitoring PPVD may be important in diagnosing suspected glaucoma patients or following glaucoma patients in cases with diseases that adversely affect GCA measurements. In addition, we believe that monitoring PPVD is useful for early diagnosis and detection of progression in disc anomalies. Our findings that VF tests showed higher correlation with PPVD measurements than with RNFLT or GCA are important in terms of clinical approach. In advanced cases with a base effect in structural analysis or incompatibility of the VF, OCTA may be especially useful as a reliable examination in follow-up.

Ethics

Ethics Committee Approval: Başkent University Medical and Health Sciences Research Board (number: 94603339-604.01.02/date: 19.02.2019).

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Authorship Contributions

Concept: S.S.G., Ş.C., A.A., Ü.E., Design: S.S.G., Ş.C., A.A., Ü.E., A.S.S., Data Collection or Processing: S.S.G., Ş.C., A.A., Ü.E., A.S.S., M.Y.Ç., Analysis or Interpretation: S.S.G., Ş.C., A.A., Ü.E., A.S.S., M.Y.Ç., Literature Search: S.S.G., Ş.C., A.A., Ü.E., A.S.S., Writing: S.S.G., Ş.C., A.A., Ü.E., A.S.S.

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Original Article

Clinical Relevance of Choroidal Thickness in Obese and Healthy Children: A Machine Learning Study

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Abstract

Objectives: To analyze the effect of macular choroidal thickness (MCT) and peripapillary choroidal thickness (PPCT) on the classification of obese and healthy children by comparing the performance of the random forest (RF), support vector machine (SVM), and multilayer perceptrons (MLP) algorithms.

Materials and Methods: Fifty-nine obese children and 35 healthy children aged 6 to 15 years were studied in this prospective comparative study using optical coherence tomography. MCT and PPCT were measured at distances of 500 µm, 1,000 µm, and 1,500 µm from the fovea and optic disc. Three different feature selection algorithms were used to determine the most prominent features of all extracted features. The classification efficiency of the extracted features was analyzed using the RF, SVM, and MLP algorithms, demonstrating their efficacy for distinguishing obese from healthy children. The precision and reliability of measurements were assessed using kappa analysis.

Results: The correlation feature selection algorithm produced the most successful classification results among the different feature selection methods. The most prominent features for distinguishing the obese and healthy groups from each other were PPCT temporal 500 µm, PPCT temporal 1,500 µm, PPCT nasal 1,500 µm, PPCT inferior 1,500 µm, and subfoveal MCT. The classification rates for the RF, SVM, and MLP algorithms were 98.6%, 96.8%, and 89%, respectively.

Conclusion: Obesity has an effect on the choroidal thicknesses of children, particularly in the subfoveal region and the outer semi-circle at 1,500 µm from the optic disc head. Both the RF and SVM algorithms are effective and accurate at classifying obese and healthy children.

Keywords: Choroidal thickness, feature selection, machine learning, obese children, optical coherence tomography

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Introduction

Childhood obesity is an exceedingly prevalent health issue in the world. The World Health Organization (WHO) has declared obesity as an "escalating global epidemic."[1] Worldwide, 22 million children under the age of 5 years and 150 million school-age children have been reported to be severely overweight, with the prevalence of childhood obesity estimated to be 10%.[2] While there are several parameters to indicate a child's nutrition and growth status, the parameter recommended by WHO is the Z-score. The Z-score system displays a set of standard deviations (SD) from the reference median or mean. It allows more accurate assessments by standardizing measurements based on age and gender.[3] The Z-score system can be used to calculate a number of anthropometric values such as weight-for-age Z-scores, height-for-age Z-scores (HAZ), weight-for-height Z-scores, and body mass index-for-age Z-scores (BMIZ). Body mass index (BMI) is the most frequently used metric in ophthalmological research to define children's nutrition and development. However, BMIZ has been reported to be the most helpful technique for assessing obesity.[4]

Obesity has been associated with multiple ocular diseases, including cataract, glaucoma, dry eye, diabetic retinopathy, and age-related macular degeneration.[5,6,7] Although the reason for the relationship between obesity and eye diseases is unclear, it is thought to be related to obesity-related chronic oxidative stress, endothelial dysfunction, and vascular damage.[6] Changes in choroidal thickness are also observed in various systemic diseases, including diabetes, hypertension, and endocrine diseases.[8,9] There are a few studies on the effects of obesity on the eyes, but no detailed assessment of macular choroidal thickness (MCT) and peripapillary choroidal thickness (PPCT) has been conducted.[10,11,12]

Due to advances in computing technology, artificial intelligence has begun to replace conventional parametric tests in data analysis. Machine learning, the most important subset of artificial intelligence, makes it possible to interpret information, classify data, and make predictions for the future by analyzing the structures and texture patterns of a large number of computer data.[13,14] Machine learning algorithms have been found to be more efficient, effective, and accurate than conventional statistical methods in the analysis of a large number of complex data.[13,15,16]

The random forest (RF) algorithm is a grouping, correlation, and other task-specific ensemble learning process.[17] Support vector machine (SVM) is a regulated classification algorithm with learning techniques for classification and correlation analysis. The SVM algorithm successfully allows multidimensional and nonlinear classifications.[18] Multilayer perceptrons (MLP) is a well-known correlation algorithm for determining the relationship between a continuous dependent variable and two or more independent variables.[19]

Several image classification studies have been conducted in the field of ophthalmology to classify different eye conditions. Dong et al.[20] conducted a study on eye state estimation with various feature sets using RF, random ferns, and SVM and reported high success with random forest/ferns. In another study, Agarwal et al.[21] demonstrated the feasibility of a multilayer-based methodology in detecting cataracts with a success rate of 94% and 75% with SVM and MLP, respectively. Improta et al.[22] studied the eye-tracking patterns of newborns acquired by electrooculography and infrared oculography to detect congenital nystagmus. They demonstrated the feasibility of a regression analysis performed through machine learning algorithms like RF, logistic regression tree, gradient boosted tree, K-nearest neighbor, MLP, and SVM to detect variables related to congenital nystagmus. Avilés-Rodríguez et al.[23] performed a quality assessment of eye fundus images acquired by digital fundoscopy with topological data analysis and machine learning methods like SVM, decision tree, k-NN, random forest, logistic regression (LoGit), and MLP. da Cruz et al.[24] studied dry eye syndrome classification using machine learning algorithms like SVM, RF, naive Bayes, MLP, random tree, and RBF Network and reported the highest performance using the RF classifier (97% accuracy).

In this study, we examined and compared the performance of RF, SVM, and MLP algorithms in the classification of obese and healthy children based on differences in MCT and PPCT. We aimed to examine the impact of childhood obesity on choroidal thickness and to recognize early clinical changes that could pose a risk for multiple ocular diseases by using machine learning algorithms, a modern method of analysis.

Materials and Methods

This research was reviewed by an independent ethical review board and conformed to the principles and applicable guidelines for the protection of human subjects in biomedical research.

In this prospective comparative study, healthy and obese children between 6 and 15 years of age who presented to the departments of pediatrics and ophthalmology for routine follow-up were recruited from 1 June 2020 to 1 December 2020. The exclusion criteria were as follows: presence of chronic diseases such as diabetes, hypertension, heart disease, and obstructive sleep apnea syndrome; history of any medication use; ocular diseases such as strabismus, cataracts, glaucoma, amblyopia, uveitis, optic disc anomaly, and retinal disease; history of prior eye surgery; more than 2 diopters of spherical or cylindrical refractive error; corneal, lens, or vitreous opacity which does not allow quality optical coherence tomography (OCT) imaging; and insufficient cooperation for OCT imaging.

Physical Examination

Height and weight measurements were taken using a digital scale and a wall-mounted Harpender stadiometer. Z-scores were determined using the WHO AnthroPlus software (www.who.int/tools/growth-reference-data-for-5to19-years/application-tools). Obesity was defined as greater than +2 SD, while normal weight was defined as between 1 and +1 SD for both BMIZ and HAZ.[3] After a resting period, blood pressure was measured using an automatic sphygmomanometer (Omron M2 HEM7121E, Omron Healthcare Co, Japan) at least three times within a 10-minute period. Blood pressure was measured as the average of a total of three consecutive measurements taken after the required resting time. Children with systolic and/or diastolic blood pressure levels greater than the 95th percentile were defined as hypertensive.[25]

Ophthalmological Examination

A detailed ophthalmological examination, including measures of best-corrected visual acuity, spherical equivalent, slit-lamp biomicroscopy, intraocular pressure (IOP), central corneal thickness (CCT), axial length (AXL), and anterior chamber depth (ACD), and OCT imaging were performed for each participant by an experienced ophthalmologist. Only the participants' right eyes were included in the study. Autokeratorefractometry (Topcon KR-800, Topcon Medical Systems, Inc., Fukuoka, Japan) was used for refractive measurements. IOP was measured using Goldmann applanation tonometry and CCT was measured using a non-contact tonopachymeter (NT-530P, Nidek Co., Gamagori, Japan). AXL and ACD were measured using optic biometry (Nidek Axial Length-Scan, Nidek Co., Gamagori, Japan). Retinal and choroidal thicknesses were assessed using Spectralis OCT (Cirrus HD OCT, Carl Zeiss Meditec, Dublin, CA, USA).

All OCT imaging and evaluations were performed by the same experienced ophthalmologist without pupil dilatation. All examinations were performed between 9:00 and 11:00 a.m. to reduce diurnal variances. Retinal thickness and mean ganglion cell layer and inner plexiform layer (GCL + IPL) thickness were measured using automated segmentation values of the Spectralis OCT system with a macular cube position of 512x128. The OCT HD 1-line-EDI protocol's high-resolution scan through the fovea was used for MCT measurements. Choroidal thickness

was assessed manually from the outer edge of the hyperreflective line corresponding to the retinal pigment epithelium to the inner layer of the sclera. MCT measurements were performed at the foveal center and at distances of 500 µm, 1,000 µm, and 1,500 µm nasally and temporally from the foveal center. For PPCT assessment, scans were carried out in vertical and horizontal planes through the middle of the optic disc using the OCT HD 5-Line Raster-EDI protocol.[26] In this scan, the optic disc is divided into two equal sections in both the horizontal and vertical planes. Then, in each of the nasal, temporal, superior, and inferior regions, PPCT measurements were taken at distances of 500 µm, 1,000 µm, and 1,500 µm from the optic disc margin (Figure 1). Both MCT and PPCT measurements were performed at 100% magnification by two masked ophthalmologists (E.B., O.D.) during different sessions for inter-observer reproducibility. The OCT Disc Cube 200x200 protocol was used for retinal nerve fiber layer thickness (RNFLT) and cup-to-disc ratio analysis. Superior, inferior, nasal, temporal, and average RNFLT values were calculated automatically.

Data Analysis

Feature Extraction and Selection

We manually measured all the features considered significant and tested whether these parameters validated our hypothesis or not. All of the manually extracted features are given in Table 1.

Feature selection techniques are based on the procedure of selecting the most important parameters. Feature selection primarily focuses on removing non-informative or irrelevant predictors from the model to minimize the number of parameters. The classification efficiency of different systems is influenced by their capabilities in data classification. In order to produce an easier, faster, and efficient classification system, we used three feature selection algorithms: variable ranking (VR), correlation feature selection (CFS), and principal component analysis (PCA). All the extracted features were entered into the VR, CFS, and PCA algorithms, and the most prominent features were selected to form the feature vector. This feature vector is used as an input for the classification algorithms (Figure 2).

Classifiers for Machine Learning

After the feature selection process, we looked at how well RF, SVM, and MLP performed with the selected prominent features and compared them to see if they could differentiate between obese and healthy children. We analyzed and compared the efficiency of RF, SVM, and MLP based on selected features. The efficiency of the different algorithms can vary, since they are structured differently. RF works through building a large number of decision trees during training and then extracting the test.[17,18] The SVM algorithm uses a training dataset to assign characteristics to just one or another subclass, making it a binary and linear classifier that cannot be predicted.[18] MLP is often used to determine which variable has the largest influence on the expected output and which variables relate to each other.[19]

Artificial intelligence-based categorization systems may be measured using precision (positive predictive), recall (sensitivity), and F-measure. Unlike precision, which only looks at correct positive predictions, recall also looks at positive predictions that did not come true. The F-measure gives us the harmonic mean of the values of precision and recall. The primary purpose of utilizing the F-measure value is to avoid selecting an inappropriate model of non-uniformly distributed datasets. The F-measure is a method for combining precision and recall into a single measure that includes all qualities. We conducted kappa analysis to assess the reliability and accuracy of our measurements. The kappa value ranges from 0 to +1. System reliability improves as the kappa value approaches 1.[27]

Results

This study included 59 obese children (35 girls, 24 boys) as the study group and 35 healthy children (21 girls, 14 boys) as the control group.

The CFS algorithm produced the most successful classification results among the three different feature selection methods. The CFS algorithm determined that subfoveal choroidal thickness is the most distinguishing feature, along with PPCT measurement locations including temporal 500 µm, temporal 1,500 µm, nasal 1,500 µm, and inferior 1,500 µm. In addition to these

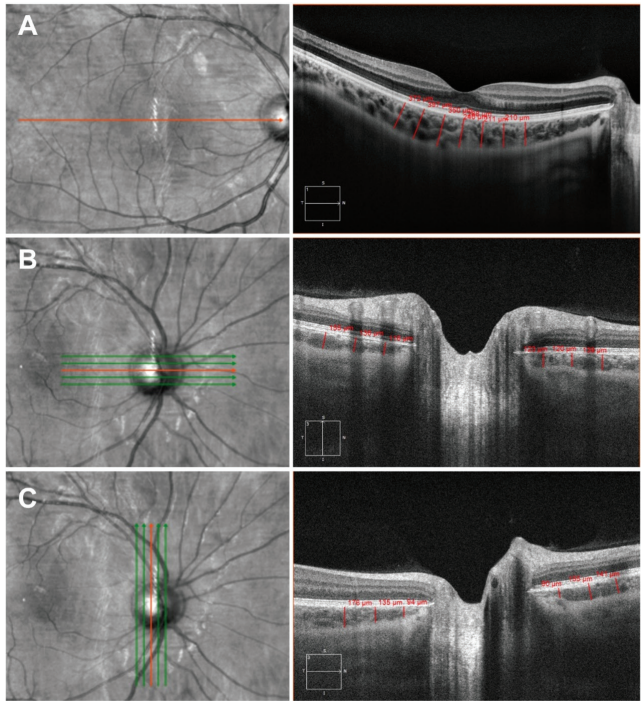

Figure 1. Example of macular and peripapillary choroidal thickness measurements (right eye). A) Macular choroidal thickness was measured at the central fovea (left panel: line denotes where the scan was taken relative to the fundus; right panel: lines show the measurement sites in the nasal (left) and temporal (right) quadrants. B) Peripapillary choroidal thickness measurements on the horizontal plane through the center of the optic disc (left panel: lines denote where the scan was taken relative to the fundus; right panel: lines show the measurement sites in the nasal (left) and temporal (right) quadrants. C) Peripapillary choroidal thickness measurements in the vertical plane through the center of the optic disc (left panel: lines denote where scan was taken relative to the fundus; right panel: lines show the measurement sites in the superior (right) and inferior (left) quadrants)

Table 1. All extracted features

Physical examination-based features	Ocular examination-based features	OCT imaging-based PPCT features	OCT imaging-based MCT features	OCT imaging-based other features
Age	Spherical equivalent	PPCT temporal 500	MCT fovea	GCL + IPL complex thickness
Sex	AXL	PPCT temporal 1000	MCT temporal 500	MT
Height	ACD	PPCT temporal 1500	MCT temporal 1000	Average c/d ratio
Weight	IOP	PPCT nasal 500	MCT temporal 1500	Vertical c/d ratio
BMI	Pachymetry	PPCT nasal 1000	MCT nasal 500	RNFLT temporal
BMIZ		PPCT nasal 1500	MCT nasal 1000	RNFLT nasal
HAZ		PPCT superior 500	MCT nasal 1500	RNFLT superior
Systolic BP		PPCT superior 1000		RNFLT inferior
Diastolic BP		PPCT superior 1500		RNFLT average
		PPCT inferior 500		
		PPCT inferior 1000		
		PPCT inferior 1500		

ACD: Anterior chamber depth, AXL: Axial length, BP: Blood pressure, BMI: Body mass index, BMIZ: BMI-for-age Z-score, c/d: Cup-to-disc, GCL + IPL: Ganglion cell layer + inner plexiform layer, HAZ: Height-for-age Z-score, IOP: Intraocular pressure, MCT: Macular choroidal thickness, MT: Macular thickness, OCT: Optical coherence tomography, PPCT: Peripapillary choroidal thickness, RNFLT: Retinal nerve fiber layer thickness

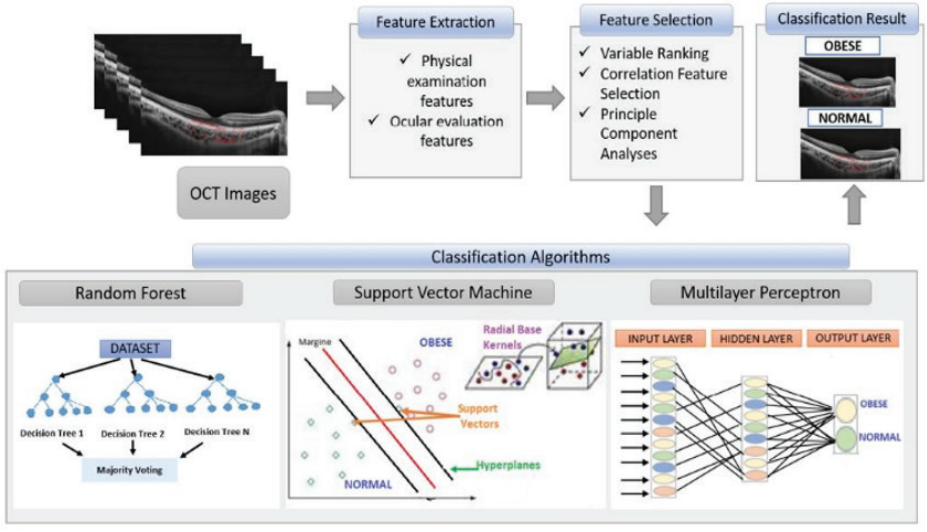

Figure 2. Flow chart of the proposed recognition system

features, the PCA algorithm selected the spherical equivalent value feature. However, when the spherical equivalent feature was absent, the classification results showed a higher success rate.

A 10-fold cross-validation process was used to test the stability and reliability of the RF, SVM, and MLP algorithms. The dataset was divided into two sections, with 70% of the data used for training and 30% for testing. To reduce selection bias, random sampling was conducted ten times to generate separate training and testing sets from the dataset.

The confusion matrix and classification rates of the RF, SVM, and MLP algorithms to classify children as normal or obese according to choroidal thickness are shown in Table 2. The overall accuracy rate of our system was 98.9% based on RF, 96.8% based on SVM, and 89.4% based on MLP.

Although the RF and SVM algorithms were equally successful at classifying the healthy group, RF was more successful in tagging the obese group. While the RF algorithm identified all obese data sets correctly, the SVM algorithm incorrectly classified two obese datasets as healthy. The BMIZ values of misclassified children were respectively 2.01 and 2.02. The thickness of the choroidal layer differed between obese and healthy children, and this difference was crucial in classifying groups using both the RF and SVM algorithms.

Despite using different learning rates and architecture, success with the MLP algorithm only increased from 85.83% to 89.36%. The reason for this small change is most probably because the dataset is limited, falls into the local extremum, and lacks spatial information.

The overall precision rate was high for RF (98.9%) and SVM (96.8%) but was relatively unsatisfactory for the MLP system (89.4%). Similarly, the overall F-measurement results of RF and SVM were both high (98.9% and 96.8%, respectively), whereas the result of MLP was low (89%). The overall recall rates for the RF and SVM systems were also 98.9% and 96.8%, respectively.

However, recall values for the obese group for the RF and SVM systems were 100% and 96.6%, respectively, which confirms the power of the proposed system's capability to recognize choroidal thickness measurements (Table 2). The average recall rate for the MLP system was 89.4%. However, the recall values of the obese and healthy groups were 98.3% and 74.3%, respectively (Table 2).

Reliability analysis yielded kappa coefficients of 0.9771, 0.9305, and 0.7600 for RF, SVM, and MLP, respectively.

Discussion

According to the findings of the current study, obesity had an effect on choroidal thickness at specific measurement regions but not at all measurement sites. The results suggest that obesity-related metabolic alterations affect choroidal thickness, particularly in the subfoveal region and the outer semi-circle at 1,500 µm from the optic disc head. This study is noteworthy because it not only comprehensively assessed choroidal thickness in obese children, but also utilized machine learning techniques in its analysis.

There are a few studies in the literature that assess the impact of childhood obesity on ocular structures. Baran et al.[10] found that obese children had higher IOP and lower RNFLT than healthy children and reported that childhood obesity may contribute to the development of glaucoma. They assessed choroidal thickness in the central subfoveal region alone and discovered no statistically significant differences. However, they did not conduct a comprehensive evaluation of MCT and PPCT. Bulus et al.[11] determined that obese children had thicker MCT than healthy children, but they did not evaluate PPCT. Additionally, they also used the BMI SD score, which is equal to the BMIZ for childhood nutrition and growth classification reported by the WHO in 2006. Bulus et al.[11] reported a strong positive correlation between BMI SD score and subfoveal MCT. Consistent with this study, we found that subfoveal MCT is affected by obesity and is a distinguishing feature between the obese and control groups.

While there are several literature studies assessing MCT in various diseases, there are few studies evaluating PPCT. Read et al.[28] identified normal PPCT values and variations in healthy children and confirmed that myopic refractive errors cause a reduction in PPCT. Ozcimen et al.[29] documented thinning in both PPCT and MCT in chronic obstructive pulmonary diseases. They attributed the choroidal thinning to vascular resistance resulting from hypoxia. Komma et al.[30] evaluated PPCT and subfoveal choroidal thickness in healthy subjects and glaucoma patients using spectral domain OCT and swept-source OCT. They discovered that choroidal thickness was significantly thicker in glaucoma subjects than controls in the peripapillary region, but not in the macular region on swept-source OCT.

This is the first research that we are aware of that evaluates PPCT in childhood obesity. Furthermore, conventional statistical methods have been employed in previous studies, including choroidal evaluation in various disorders. There is no prior study in the current literature that evaluates both MCT and PPCT using machine learning algorithms.

In machine learning, feature selection helps boost classification efficiency by avoiding over-fitting, creating a time-saving model, and making the designed model more human-friendly. There are

Table 2. Classification results of obese and healthy children based on choroidal thickness by algorithm

	TP rate	FP rate	Precision	Recall	F-measure	Confusion matrix	
Random forest algorithm							
Obese	1	0.029	0.983	1	0.992	59	0
Normal	0.971	0.000	1	0.971	0.986	1	34
Weighted average	0.989	0.018	0.990	0.989	0.989		
Support vector machine algorithm							
Obese	0.966	0.029	0.983	0.966	0.974	57	2
Normal	0.971	0.034	0.944	0.971	0.958	1	34
Weighted average	0.968	0.031	0.968	0.968	0.968		
Multilayer perceptrons algorithm							
Obese	0.983	0.257	0.866	0.983	0.921	58	1
Healthy	0.743	0.017	0.963	0.743	0.839	9	26
Weighted average	0.894	0.168	0.902	0.894	0.890		

TP: True positive, FP: False positive

several feature selection approaches in the literature to minimize the number of features for classification purposes. Different subsets can be created with each feature selection method. We ran all of the data through a feature selection process using three different algorithms: VR, CFS, and PCA. None of the parameters associated with MCT and PPCT were excluded in any of the three analyses, and they were found to be distinctive in all of them. According to the results, obese and healthy children have significantly different choroidal thicknesses at specific measurement regions. These measurement regions were PPCT temporal 500 µm, PPCT temporal 1,500 µm, PPCT nasal 1,500 µm, PPCT inferior 1,500 µm, and the subfoveal region. In the PCA algorithm, spherical equivalent value was chosen in addition to the distinguishing features chosen in the CFS algorithm. There was no statistically significant difference between the two groups' spherical equivalent values. The CFS algorithm outperforms PCA in classification because the spherical equivalent value was not a distinguishing feature for these groups. While machine learning algorithms identify distinct features in classification for the two groups, they do not show the relative value of these features in each group. As machine learning algorithms reveal the importance of features, classification is performed on all of the selected features.

In this study, we compared the results of three different classification algorithms (RF, SVM, and MLP) because it is difficult to predict which machine learning algorithm will perform better in classification. We selected RF because it is a good comparison and classification technique and can detect outliers very well. SVM is a very robust technique for solving high-dimensional problems and creating accurate classifications. MLP is an accessible technique with the ability to create a simple architecture, easily build it, and quickly calculate the model. The risk of falling into the local extremum, weak overfitting skills, a lack of theoretically-based rigid design programs, and difficulty managing the training program are disadvantages of the MLP algorithm. SVM may be more determinant in some cases, even though the RF algorithm is generally more successful in classification. We had several difficulties applying the SVM and MLP algorithms because of the limited and unbalanced datasets used in this study. To overcome this challenge, we focused on kernel selection, which had an effect on the kernel's success in implementing the SVM algorithm. We used polynomial and radial base kernels to improve classification efficiency by reducing our margin of error. Additionally, the success of the MLP algorithm was influenced by the network structure. The more complicated the network's structure, the more successful it will be. However, we did not increase the number of layers in order to reduce the margin of error.

While RF produces better results against outliers and noise than SVM, it is not as successful in handling the dataset imbalance problem. Although our dataset was slightly unbalanced, the results with RF were quite successful. MLP was found to be less successful than SVM and RF in the classification according to choroidal thickness.

The MLP algorithm had the highest rate of misclassification of all of the classification techniques. The MLP algorithm misclassified ten children, three of whom were also misclassified by the SVM algorithm. We found no similarities in terms of features such as height or weight in cases misclassified by the MLP algorithm. In terms of group classification, we discovered that the SVM algorithm outperformed the MLP algorithm. The main reason for misclassification based on the SVM algorithm may be that the children were at the threshold of obesity according to their BMIZ values. As a result, the classification success of the SVM algorithm is higher in obese cases with high BMIZ values.

The performance of machine learning algorithms, as well as the complexity of the models used, are influenced by the quality and quantity of data. To the best of our knowledge, there is no open dataset in the literature that is comparable to our dataset. The drawback of our analysis is the limited size of the dataset. However, the majority of medical research faces difficulty in achieving a sufficient number of cases. Obtaining large quantities of high-quality data for medical research is a time-consuming and difficult task. There is medical research in the literature that uses machine learning algorithms with small datasets. Ruiz Hidalgo et al.[31] used machine learning algorithms to classify keratoconus using five Pentacam-derived parameters of 131 eyes. An et al.[32] developed classification criteria that could aid in the clinical management of glaucoma by using machine learning algorithms to classify 163 glaucomatous optic discs. Cartes et al.[33] evaluated the variability of tear osmolarity in 20 patients with dry eye using machine learning techniques. It has been demonstrated that machine learning algorithms can conduct self-diagnosis and classification analyses of OCT images with high accuracy, speed, and consistency.[34] However, in the classification tests, we measured kappa values to ensure that the small dataset did not affect the reliability of our results and to maximize success. The kappa value is a measure that contrasts the observed precision with the predicted precision (random chance). This is a far more reflective indicator of model efficiency. Kappa values were measured as 0.9771, 0.9305, and 0.7600 for the RF, SVM, and MLP analyses, respectively. According to the kappa statistics, RF is the most accurate test, but the reliability of SVM is also very similar to RF. Despite the limited number of datasets, kappa analyses showed that both RF and SVM were very successful and reliable in the classification of obese and healthy children.

Conclusion

The current study indicates that MCT and PPCT differ in obese and healthy children and are effective in the categorization of these two groups using machine learning algorithms, especially when the RF or SVM algorithms were used. Additionally, obesity was shown to impact choroidal thickness in certain regions when compared to healthy children. The current study emphasizes the importance of subfoveal MCT as well as PPCT measurements in some regions (including temporal 500 µm, temporal 1,500 µm,

nasal 1,500 µm, and inferior 1,500 µm) in classifying children as obese or healthy. To improve classification performance, further deep learning studies with larger datasets are needed.

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Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Biruni University (document number: 2020/40-06).

Informed Consent: Informed consent and oral consent was obtained from all individual participants and/or their legal guardians.

Peer-review: Externally peer reviewed.

Authorship Contributions

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Original Article

Regional Analysis of Inner Retinal Layer Changes in Multiple Sclerosis with and without Optic Neuritis

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Abstract

Objectives: The study aimed to investigate inner retinal changes in multiple sclerosis (MS) patients by comparing them with healthy controls. The study also aimed to assess regional differences of inner retinal layer involvement in eyes with and without optic neuritis (ON).

Materials and Methods: This retrospective, cross-sectional study consisted of 141 eyes of 74 relapsing-remitting MS patients and 80 eyes of 40 healthy controls. The study group was separated into two subgroups according to the presence of ON history. Peripapillary retinal nerve fiber layer (pRNFL) thickness, total macular thickness, and thicknesses of the macular retinal nerve fiber layer (mRNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), and inner nuclear layer were compared between the MS and healthy control groups and between eyes with and without ON history.

Results: Mean pRNFL, total macular, mRNFL, GCL, and IPL thicknesses were significantly thinner in the MS group than in the control group ($p<0.001$) and in eyes with ON compared to those without ON ($p<0.05$). Comparison of inner retinal layer thicknesses in the inner 3-mm ring subfields of the ETDRS grid revealed significant thinning in all subfields of the GCL and IPL of eyes with ON ($p<0.05$). The inferior subfield demonstrated the highest difference.

Conclusion: The study demonstrated that GCL and IPL thinning is a robust and reliable biomarker in all MS patients. The thinning was significantly greater in eyes with ON than in eyes without ON. The study also documented that the inferior region showed significantly greater GCL and IPL thinning in eyes with previous ON attacks.

Keywords: Multiple sclerosis, optic neuritis, optical coherence tomography, retinal ganglion cell, retinal nerve fiber

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Introduction

Multiple sclerosis (MS) is a degenerative disorder affecting the brain and spinal cord. It is a chronic demyelinating disease and frequently involves the visual pathways. Inflammation of the optic nerve, termed optic neuritis (ON), can be the initial presentation of MS. About 28% of patients with ON develop MS within 10 years.[1] In addition, autopsy findings revealed 90% optic nerve involvement in over 90% of MS patients.[2] Another postmortem study detected inner retinal atrophy in about 79% of MS patients and correlated the severity of retinal atrophy with overall brain weight at the time of autopsy.[3]

Optical coherence tomography (OCT) is a simple, cost-effective, and reliable tool for retinal visualization. OCT enables the acquisition of retinal images in three dimensions and cross-sections. It measures all retinal layers separately, including the peripapillary retinal nerve fiber layer (pRNFL). Retinal findings on OCT are strongly associated with brain tissue changes in MS patients.[4] In addition, several studies have confirmed the important place of OCT in both the diagnosis and monitoring of MS, even in the absence of ON.[5,6]

This study primarily aimed to investigate changes in the inner retinal layers in MS patients with and without ON compared to healthy controls. The secondary aim was to assess regional differences in the inner retinal layers in MS patients.

Materials and Methods

This retrospective, cross-sectional study was approved by the Scientific Research Ethics Committee of the Health Sciences University Türkiye (date: March 23, 2021, no: E-46418926-050.01.04-1592) and was conducted according to the principles of the Declaration of Helsinki. People with MS were referred

from the MS unit of the neurology department for routine ophthalmological assessments. MS was diagnosed by a specialist neurologist based on the 2010 McDonald criteria. The study group was separated into two subgroups, those with and those without a history of ON. Patients with an ON history of less than six months were excluded. Healthy people who presented to the outpatient clinic for routine eye examination or because of refractive error formed the control group.

Exclusion criteria were glaucoma, refractive errors more than 4 diopters, any retinal disorders affecting the optic nerve and macular layer structure, any ophthalmological disorder that prevented good quality retinal imaging (e.g., corneal opacities, dense cataract, nystagmus), and a history of intraocular surgery other than uncomplicated phacoemulsification surgery performed at least 6 months earlier.

All participants underwent a complete ophthalmologic examination. Retinal spectral-domain OCT (SD-OCT) was done with Spectralis (software version 6.16.2, Heidelberg Engineering, Heidelberg, Germany). Images were obtained by a trained technician. Images precisely centered on the fovea with good quality were recorded. Scanning was performed in a 30x20 degree cube consisting of 25 raster lines at 240 µm intervals. Retinal layers were determined automatically (Figure 1a). Thicknesses of the total macula and inner layers including the macular retinal nerve fiber layer (mRNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), and inner nuclear layer (INL) were recorded in each of the nine subfields in the Early Treatment Diabetic Retinopathy Study (ETDRS) grid (Figure 1b). The mean total macular thickness and the thicknesses of each inner retinal layer were obtained from the average of the thicknesses of the nine subfields. Volumes were also calculated automatically by SD-OCT. Mean peripapillary RNFL (pRNFL) thickness was determined from the average of sixteen successive B scans surrounding the optic disc (diameter 3.5 mm, 768 A-scans) (Figures 1c and 1d).

Statistical Analysis

The data were analyzed statistically using IBM SPSS version 20.0 (IBM Corp, Armonk, NY, USA) software. The fit of the data to normal distribution was determined visually and analytically (Kolmogorov-Smirnov test). Descriptive statistics for variables with normal distribution were presented as mean and standard deviation. Comparisons between two groups were made using independent samples t-test. One-way analysis of variance (ANOVA) was used to compare multiple groups. Welch statistics were used when the variances were not homogeneous. Tamhane's T2 or LSD tests were used in post-hoc analyses according to whether the variances were homogeneous or not. Comparison of categorical variables was made with Pearson chi-square test. A p-value less than 0.05 was accepted as statistically significant.

Results

The study included 141 eyes of 74 patients with relapsing-remitting MS and 80 eyes of 40 healthy controls. Gender and age characteristics were similar in the MS and control groups, while the MS group had significantly lower visual acuity ($p<0.001$). The mean MS duration was determined as 10.88±7.45 years. Demographic properties, Expanded Disability Status sale scores, and best-corrected visual acuity (BCVA) of the groups are summarized in Table 1.

Within the MS group, 46 eyes had a positive history of ON and 95 eyes had a negative history. MS patients with ON were 5.48 years younger on average than those without ON ($p<0.05$). Although the mean BCVA in patients with ON was 0.07 (decimal) lower than that in patients without ON, this difference was not statistically significant ($p=0.126$). The mean number of ON attacks was 1.46±0.88.

pRNFL measurements were significantly thinner in the MS group than in the control group ($p<0.001$) (Table 2). When the subgroups with and without ON were compared with each

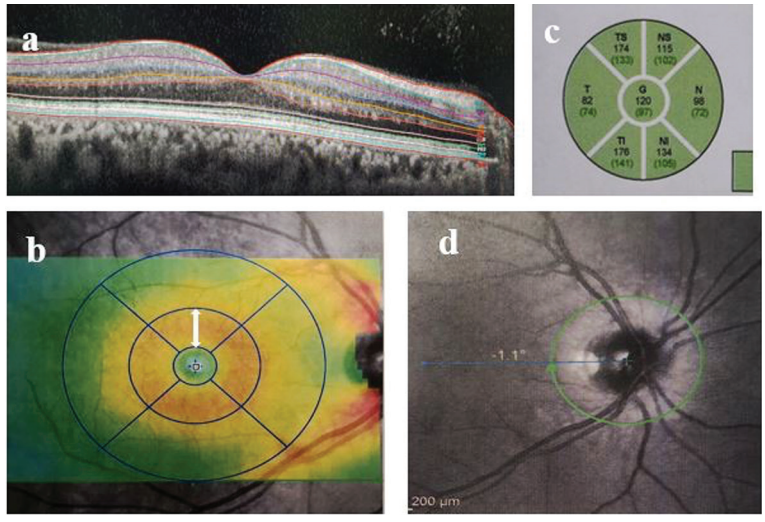

Figure 1. a) Automatic segmentation of the macular retinal layers by spectral domain optical coherence tomography; b) Nine subfields of the macula in the ETDRS (Early Treatment Diabetic Retinopathy Study) grid. The white double arrow shows inner and outer boundaries of the inner 3-mm annulus; c,d) Peripapillary retinal nerve fiber measurement

other and the control group, pRNFL measurements also showed significant differences between all groups (p<0.05, p<0.001, p<0.001) (Table 2).

The mean total macular, mRNFL, GCL, and IPL thicknesses were significantly thinner in the MS group compared to the control group (p<0.001) (Table 2). The mean INL thickness was greater in the MS group, but the difference was insignificant (p=0.171) (Table 2). Consistent with the thickness results, mean macular, mRNFL, GCL, and IPL volumes were statistically lower in the MS group compared to the control group (p<0.001), while the mean INL volume did not differ significantly (p=0.067) (Table 2).

The subgroups with ON and without ON demonstrated significant thinning and volume loss in the total macula, mRNFL, GCL, and IPL in comparison with the control group (p<0.001) (Table 2). The mean INL thickness and volume were thicker in both MS subgroups than in the control group, but only the subgroup with ON showed a statistical significance (p<0.05) (Table 2). When the subgroups with and without ON were compared with each other, the thicknesses and volumes of all layers except the INL were significantly lower in the subgroup with ON (p<0.05) (Table 2).

Comparison of total macular and inner retinal layer thicknesses in the inner 3-mm ring subfields of the ETDRS grid revealed significant thinning in all subfields in the GCL and IPL of eyes with ON (p<0.05) (Figure 2a, b). The greatest difference was in the inferior subfields of the GCL and IPL (6.481 µm, p<0.001; 4.115 µm, p<0.001, respectively). Total macular thickness showed statistically significant thinning in the inferior, nasal, and temporal subfields (p<0.05) but not the superior subfield (p=0.071) (Figure 2a). mRNFL showed no significant differences between the two subgroups in any subfield (Figure 2b). The INL was thicker in all subfields in eyes with ON, with statistically significant differences in the superior, temporal, and nasal subfields (Figure 2b).

BCVA (decimal) showed weak to moderate positive correlation with total macular thickness (r=0.338, p<0.001) and pRNFL (r=0.297, p<0.001), mRNFL (r=0.425, p<0.001), GCL (r=0.472, p<0.001), and IPL thickness (r=0.488, p<0.001).

Discussion

The present study demonstrated significant thinning in all inner retinal layers except the INL in the eyes of people with MS. This study also revealed that GCL and IPL thinning was greater in eyes with ON compared to those without ON, and this thinning was significantly greater in some regions.

OCT measurements of the retina have been proposed as biomarkers in the diagnosis and follow-up of MS.[7] pRNFL and macular GCL/IPL measurements in particular were recommended for MS diagnosis and monitoring.[5,8] The cause of retinal changes was initially thought to be retrograde neurodegeneration secondary to demyelination.[9] A recent study also supported the mechanism of anterograde neurodegeneration affecting the visual pathways.[10] Pietroboni et al.[11] found significant reductions in mRNFL, GCL, IPL, and GCL + PL thickness in the very early clinical stages of MS without a history of ON. The current study showed significant thinning of the pRNFL, mRNFL, GCL, and IPL in MS patients compared with healthy controls, independently of ON history. These findings are consistent with studies suggesting there is both anterograde and retrograde transsynaptic neurodegeneration in MS.

Comparison based on ON history showed that total macular, pRNFL, mRNFL, GCL, and IPL thicknesses were significantly reduced in eyes with ON. On the other hand, the change in INL did not show statistical significance. Consistently, the total macular, mRNFL, GCL, and IPL volumes showed statistically significant reductions in ON eyes. Similarly, Seitz et al.[12] found a significant decrease in total macular, mRNFL, and GCL + PL umes in patients with ON compared to those without ON. The study by Seitz et al.[12] included patients with a mean disease duration of 2.2±3.5 years, whereas our study included late-stage cases with a mean disease duration of 10.88±7.45 years. Another study also reported significant thinning of the total macula, mRNFL, GCL, and IPL in eyes with ON compared to those without ON, in line with the current study.[13]

Table 1. Demographic characteristics and best-corrected visual acuity levels of the study and control groups

	Multiple sclerosis (n=141 eyes)	**Control (n=80 eyes)**	**p**	**ON– (n=95 eyes)**	**ON+ (n=46 eyes)**	**Control (n=80 eyes)**	**p**
Gender, n (%)	Male: 60 (42.6) Female: 81 (57.4)	Male: 40 (50) Female: 40 (50)	0.285*	Male: 40 (42.1) Female: 55 (57.9)	Male: 20 (43.5) Female: 26 (56.5)	Male: 40 (50) Female: 40 (50)	0.558*
Age (years)	41.6±10.0	41.8±14.0	0.934**	43.44±9.78	37.96±9.74	41.8±14.0	[1]**0.031**‡ [2]0.762‡ [3]0.205‡
BCVA (decimal)	0.94±0.19	1.00±0.00	<0.001**	0.96±0.14	0.89±0.25	1.00±0.00	[1]0.332‡ [2]**0.046**‡ [3]**0.033**‡
Expanded Disability Status Scale	4.52±1.42	-		4.52±1.31	4.50±1.70	-	0.937**

BCVA: Best-corrected visual acuity, ON: Optic neuritis
[1]ON- vs. ON+, [2]ON- vs. control, [3]ON+ vs. control. *Pearson chi-square test, **Independent samples t-test, ‡One-way ANOVA, Welch, post-hoc Tamhane's T2

Table 2. Comparison of peripapillary retinal nerve fiber layer thickness and total macular and inner retinal layer thicknesses and volumes between the control group and the multiple sclerosis (MS) group overall and the MS subgroups with optic neuritis (ON+) and without optic neuritis (ON-)

	MS (n=141)	Control (n=80)	p	ON- (n=95)	ON+ (n=46)	Control (n=80)	p
pRNFL (µm)	83.34±14.79	100.59±8.43	**<0.001***	86.37±14.33	77.09±13.86	100.59±8.43	[1]0.001‡ [2]<0.001‡ [3]<0.001‡
Total macular thickness (µm)	296.02±16.71	309.50±13.03	**<0.001***	298.37±16.41	291.15±16.45	309.50±13.03	[1]0.048‡ [2]<0.001‡ [3]<0.001‡
mRNFL thickness (µm)	22.18±4.79	26.72±1.98	**<0.001***	22.72±4.85	21.14±4.55	26.72±1.98	[1]0.030† [2]<0.001† [3]<0.001†
GCL thickness (µm)	32.02±6.39	40.65±3.33	**<0.001***	33.27±6.15	29.61±6.23	40.65±3.33	[1]<0.001† [2]<0.001† [3]<0.001†
IPL thickness (µm)	28.45±4.69	33.68±2.35	**<0.001***	29.18±4.93	27.05±3.87	33.68±2.35	[1]0.003† [2]<0.001† [3]<0.001†
INL thickness (µm)	34.86±4.67	34.09±2.36	**0.171***	34.33±5.03	35.90±3.71	34.09±2.36	[1]0.120‡ [2]0.972‡ [3]**0.012**‡
Total macular volume (mm^3)	8.20±0.47	8.56±0.37	**<0.001***	8.27±0.48	8.06±0.43	8.56±0.37	[1]0.032‡ [2]<0.001‡ [3]<0.001‡
mRNFL volume (mm^3)	0.72±0.17	0.89±0.07	**<0.001***	0.75±0.17	0.69±0.17	0.89±0.07	[1]0.026† [2]<0.001† [3]<0.001†
GCL volume (mm^3)	0.90±0.15	1.11±0.09	**<0.001***	0.93±0.15	0.84±0.14	1.11±0.09	[1]<0.001† [2]<0.001† [3]<0.001†
IPL volume (mm^3)	0.77±0.11	0.90±0.06	**<0.001***	0.79±0.12	0.74±0.09	0.90±0.06	[1]0.007† [2]<0.001† [3]<0.001†
INL volume (mm^3)	0.98±0.12	0.95±0.06	0.067*	0.97±0.14	1.00±0.09	0.95±0.06	[1]0.419‡ [2]0.609‡ [3]**0.012**‡

pRNFL: Peripapillary retinal nerve fiber layer, mRNFL: Macular retinal nerve fiber layer, GCL: Ganglion cell layer, IPL: Inner plexiform layer, INL: Inner nuclear layer
[1]ON-vs. ON+, [2]ON-vs. control, [3]ON+ vs. control . *Independent samples t-test, †One-way ANOVA, post-hoc LSD, ‡One-way ANOVA, Welch, post-hoc Tamhane's T2

The present study also compared differences in the inner 3-mm subfields of the ETDRS grid in eyes with and without a history of ON. Regional comparison of inner retinal layer changes revealed the greatest difference in the inferior subfield. The nasal and temporal subfields followed the inferior subfield in terms of the difference in total macular, GCL, and IPL thickness between the two subgroups. Thinning of the GCL in the inferior macula has also been implicated as a sign of early glaucomatous damage.[14,15] Hood et al.[15] introduced a macular vulnerability zone to define the most susceptible area of retinal ganglion cells in early glaucoma. This zone corresponds to the inferior macula. The axons of the retinal ganglion cells in the zone extend into the inferotemporal part of the optic disc, which is known to be vulnerable to glaucomatous damage. Our finding of profound ganglion cell loss in the inferior macula may indicate a similar mechanism of optic nerve involvement in MS. Özbilen et al.[16] reported regional differences in the inner retinal layers in MS patients and consistent with our study, they observed the greatest difference in ganglion cells in the inferior 3-mm subfield of ETDRS ring in their study comparing eyes with ON and without ON.

BCVA demonstrated the highest correlation with GCL and IPL thicknesses, followed by mRNFL and total macular thickness. The lowest correlation was seen with pRNFL. Our findings corroborate previous studies reporting the robust association of GCL and IPL thinning with visual function in MS patients with and without ON history.[17,18,19] Narayanan et al.[20] observed a high correlation between multifocal visual evoked potential and GCL + IPL thickness, supporting the relation of GCL-IPL thickness to visual function in MS.

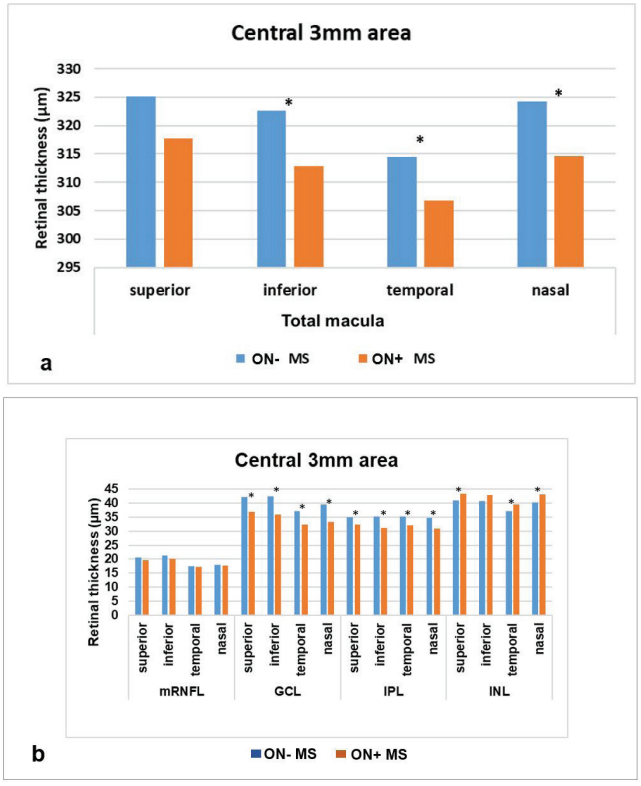

Figure 2. a) Total macular thickness in eyes with a history of optic neuritis (ON) demonstrated thinning in all inner 3-mm subfields of the ETDRS (Early Treatment Diabetic Retinopathy Study) grid. The thinning was statistically significant in the inferior, temporal, and nasal subfields; b) Comparison of inner retinal layers in the inner 3-mm subfields of the ETDRS ring. Ganglion cell layer (GCL) and inner plexiform layer (IPL) showed significant thinning in all subfields in eyes with ON history, while the inner nuclear layer (INL) showed significant thinning in the superior, temporal, and nasal subfields. Macular retinal nerve fiber layer (mRNFL) showed no significant difference in any subfield and inner nuclear layer (INL). *p<0.05

Study Limitations

The main limitation of the study is its retrospective nature. In addition, the study included cases with only one type of MS and did not compare different types.

Conclusion

Our study demonstrated that GCL and IPL thinning is a robust and reliable biomarker in all MS patients. However, the thinning in these layers was significantly greater in eyes with a history of ON than in eyes without ON. The study also documented that the inferior region showed significantly greater GCL and IPL thinning in eyes with previous ON attacks. This finding may guide future studies about the specific feature of the optic nerve involvement in MS.

Ethics

Ethics Committee Approval: This retrospective, cross-sectional study was approved by the Scientific Research Ethics Committee of the Health Sciences University Türkiye (date: March 23, 2021, no: E-46418926-050.01.04-1592) and was conducted according to the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: B.K., Ş.S., Concept: B.K., Ş.S., N.D., S.D., M.S., Design: B.K., S.D., Data Collection or Processing: B.K., Ş.S., N.D., S.D., Analysis or Interpretation: B.K., Ş.S., N.D., S.D., M.S., Literature Search: B.K., Ş.S., N.D., Writing: B.K., Ş.S., M.S.

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Review

Applications of Mitomycin C in Cornea and External Disease

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Abstract

Isolated from *Streptomyces caespitosus*, mitomycin C (MMC) has various applications in the management of corneal and external disease due to its ability to modulate cellular proliferation. It has been employed in pterygium surgery, ocular surface neoplasia, and refractive surgery. Currently, there is no definite consensus on the treatment protocols for each of the aforementioned applications. Although its benefits in the management of corneal and external diseases are promising, MMC use has potential complications including endothelial cell loss, corneal perforation, scleral melt, secondary glaucoma, iritis, and endophthalmitis. This article will review the literature regarding the use of MMC in the field of cornea and external disease and describe protocols employed with corresponding outcomes.

Keywords: Mitomycin C, pterygium surgery, photorefractive keratectomy scar, post-PRK haze

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Introduction

Mitomycin C (MMC) is an antitumor antibiotic isolated from *Streptomyces caespitosus*.[1] MMC is an alkylating agent that covalently binds to DNA, resulting in an antitumoral effect.[2] MMC inhibits DNA synthesis primarily at the G1/S phase, resulting in a decrease in cell proliferation and migration.[3] MMC was introduced in ophthalmic surgery in 1963 as an adjunct to pterygium surgery.[4] MMC is also thought to elicit apoptosis of corneal epithelial, stromal, and endothelial cells as well as Tenon's capsule fibroblasts and ocular tumor epithelial cells.[5] In addition to its application in pterygium surgery, it has uses in ocular surface tumors, refractive surgery, glaucoma drainage surgery, oculoplastic surgery, and strabismus surgery.[3] In this manuscript, we broadly review the applications of MMC in the field of cornea and external disease. More comprehensive reviews exist in the literature on each subtopic covered in this work, and thus this manuscript aims to set the groundwork for interested readers.

Pterygium Excision

Pterygium is a wing-shaped benign fibrovascular overgrowth that centripetally involves the cornea.[6] Surgical excision may be performed to preserve visual acuity, achieve cosmetic improvement, or treat ocular surface symptoms. Recurrence rates (RRs) after pterygium surgery are variable, and adaptations have been developed to minimize this complication, including the use of supplemental MMC.[7] MMC use has been shown to decrease RRs when used as an adjuvant with a variety of surgical techniques, including bare sclera excision, excision with autografting, and excision with amniotic membrane transplantation. Furthermore, MMC may be used preoperatively, intraoperatively, or postoperatively in selected cases.[8]

Bare sclera technique

Surgical removal of pterygium using the bare sclera technique without any adjuvant treatment leads to an RR as high as 88%,[9] and for this reason the technique has been largely abandoned for alternative methods. MMC has been employed as an adjuvant treatment to bare sclera excision due to this high RR. Intraoperative application of MMC at concentrations ranging from 0.01% to 0.04% for durations ranging from 30 seconds to 5 minutes has led to a significant reduction in the RRs of pterygia when using the bare sclera technique. RRs ranged from 3.33% to 42.9% when using these dosages (Table 1).[10,11,12,13,14,15,16] Differences between the treatment regimens (concentration and duration) may explain some of the variability in recurrence. However, differences in age, race, and environmental factors may also contribute to variations in RRs.

MMC has also been used preoperatively with the bare sclera technique via subconjunctival injection at a dose of 0.1 mL of 0.015-0.02%. Using this approach 1 month or 1 day before pterygium surgery has led to an RR of 0-6% (Table 2).[11,17,18] Because of the small sample size, a direct comparison may not be suitable. Further studies on the preoperative use of MMC may help assess the relationship between dose, time, and efficacy. Authors observed that 0.1 mL of 0.015% concentration is similarly effective when employed as a subconjunctival injection 1 day before surgery (1/25 eyes recurred) and applied intraoperatively (2/25 recurred).[11]

Postoperative topical MMC has also been shown to decrease RRs in the bare sclera technique. Dosages for this approach have been reported to range from 0.02% to 0.04% MMC applied topically 2 to 4 times a day for 5 to 14 days (Table 3).[9,19,20,21] In some populations, postoperative use of 0.02% MMC twice daily for 5 days following bare sclera excision was shown to be as effective as conjunctival autografting in preventing recurrence (RR of 38% and 39%, respectively).[9]

Conjunctival Autograft Technique

The conjunctival autograft technique has been employed in pterygium surgery with RRs as high as 39% in the absence of MMC.[9] MMC has been utilized intraoperatively as an adjunct to conjunctival autografting in concentrations ranging from 0.015% to 0.04%, leading to pterygium RRs ranging from 0% to 15.6% (Table 4).[18,22,23,24,25,26,27,28]

In most studies, MMC has been utilized intraoperatively when performing conjunctival autografting, although some authors have also reported utilizing MMC preoperatively or postoperatively. Gupta et al.[18] used 0.1 mL of 0.02% MMC via subconjunctival injection 1 month before surgery and achieved an RR of 3.3%. Similarly, Fakhry[22] used 0.1 mL of 0.015% MMC 1 month before surgery, observing an RR of 5.0%. Cardillo et al.[27] described the use of MMC in concentrations of 0.02-0.04%, either intraoperatively for 3 minutes or postoperatively via topical solution 3 times daily for 7 or 14 days. In this study, the RR for intraoperative MMC ranged from 4.08% to 6.66%, while postoperative MMC yielded an RR that ranged from 4.26% to 4.44%. Since no significant difference in RR reduction was observed between intraoperative or postoperative use, the authors suggested that intraoperative use should be favored since it is not subject to patient misuse or lack of compliance.[27]

While most studies report a significant decrease in RR when using MMC, a study performed in Saudi Arabia reported an RR of 15.6% when performing conjunctival autografting with 1 minute of intraoperative 0.02% MMC, versus an RR of 15.8% when performing conjunctival autografting alone, indicating some variability in practice patterns and surgical outcomes.[24] As seen in Table 4, the use of MMC generally appears to decrease RR. However, a protocol for optimal dosing and timing has not yet been established due to the differences in the populations studied and the power of the results from individual studies.

Amniotic Membrane Grafting Technique

Utilizing amniotic membrane grafting (AMG) alone without MMC to treat pterygium has led to RRs ranging from 13.8% to 72%.[29,30] MMC has been employed as an adjuvant in this technique to further reduce RR. Intraoperative use of 0.02% MMC for 2 and 3 minutes has led to an RR of 34.5% and 10.9%, respectively.[31,32] Rosen[33] reported an even lower RR of 5.8% when using 0.02% MMC intraoperatively for 60-90 seconds. As 0.5% of the eyes treated with this protocol developed scleral thinning, the exposure time was reduced to 20-30

Table 1. Intraoperative use of mitomycin C in pterygium excision using the bare sclera technique

Application time (min)	Concentration	Recurrence rate in control group (%)	Recurrence rate in treatment group (%)	Reference
0.5	0.02%	----	7.9-19.2	Cheng et al.[10]
3	0.015%	----	8	Zaky and Khalifa[11]
3	0.02%	75	42.9	Lam et al.[12]
3	0.04%	75	22.9	Lam et al.[12]
5	0.01%	38.8	3.33	Cano-Parra et al.[13]
5	0.02%	57.8	21	Yanyali et al.[14]
5	0.02%	75	8.3	Lam et al.[12]
5	0.02%	45	5	Frucht-Pery et al.[15]
5	0.02%	----	6.35-25	Avisar and Weinberger[16]
5	0.04%	75	8.6	Lam et al.[12]

seconds, after which no further cases of scleral thinning were noted.[33] Despite data indicating that MMC reduces recurrence after AMG, we cannot draw any definitive conclusions since none of the aforementioned studies had a control group. Ma et al.[34] directly compared AMG alone and AMG with intraoperative 0.025% MMC for 3 minutes and noted no significant decrease in recurrence (RR was 12.5% in the AMG alone group and 12.8% in the MMC group). Further well-designed studies are required to better understand if there is any combination of concentration and exposure time to lessen the RR of pterygium when employing the AMG technique.

Table 2. Preoperative use of mitomycin C in pterygium excision using the bare sclera technique

Dosage*	Time of application	Recurrence rate (%)	Reference
0.1 mL of 0.015%	1 day	4	Zaky et al.[11]
0.1 mL of 0.015%	1 month	6	Donnenfeld et al.[17]
0.1 mL of 0.02%	1 month	0	Gupta et al.[18]

*Administered via subconjunctival injection

Ocular Surface Tumors

Ocular Surface Squamous Neoplasia

Ocular surface squamous neoplasia (OSSN) often involves both the cornea and the conjunctiva, and includes a spectrum of four pathologies: dysplasia, intraepithelial neoplasia, carcinoma in situ, and squamous cell carcinoma.[35] MMC has been used to treat OSSN as a primary treatment, intraoperative adjuvant, and postoperatively for lesions that were not entirely resected during excision.[36,37] Topical MMC concentrations as low as 0.002% have resulted in regression of primary and recurrent tumors,[38] although dosages ranging from 0.02% to 0.04% MMC are most often used.[39,40] Typically, MMC drops are instilled 4 times a day either until resolution or in different regimens of on and off weekly cycles.[38,39,40] Prabhasawat et al.[38] reported the results of treating 7 patients with 0.002% MMC 4 times a day until tumor regression, which was observed at a mean treatment duration of 5.2 weeks. Ballalai et al.[39] described the use of 0.02% MMC 4 times a day for 28 consecutive days, achieving complete tumor regression in all patients, of which only 1 out of 23 recurred. MMC has also shown promising results in

Table 3. Postoperative use of mitomycin C in pterygium excision using the bare sclera technique

Concentration	Regimen	Recurrence rate in control group (%)	Recurrence rate in treatment group (%)	Reference
0.02%	Twice daily for 5 days	88	38	Chen et al.[9]
0.02%	Twice daily for 5 days	32	7	Hayasaka et al.[19]
0.02%	Twice daily for 5 days	---	2.6	Rachmiel et al.[20]
0.04%	Three times daily for 7 days	32	11	Hayasaka et al.[19]
0.04%	Four times daily for 14 days	60	0	Mahar and Nowakara[21]

Table 4. Use of mitomycin C in pterygium excision using the conjunctival autografting technique

Application period	Application regimen	Concentration	Recurrence rate in control group* (%)	Recurrence rate in treatment group (%)	Reference
Preoperative	0.1 mL SC injection	0.02%	----	3.3	Gupta et al.[18]
	0.1 mL SC injection	0.015%	21.1	5	Fakhry[22]
Intraoperative	1 min	0.02%	13.3	0	Frucht-Pery et al.[23]
	1 min	0.02%	15.8	15.6	Alsarhani et al.[24]
	1 min	0.025%	18	9	Wong and Low[25]
	2 min	0.02%	----	0	Wagdy et al.[26]
	3 min	0.02%	29.27	6.66	Cardillo et al.[27]
	3 min	0.04%	29.27	4.08	Cardillo et al.[27]
	5 min	0.02%	----	3	Young et al.[28]
Postoperative	Three times daily for 7 days	0.02%	29.27	4.26	Cardillo et al.[27]
	Three times daily for 14 days	0.04%	29.27	4.44	Cardillo et al.[27]

SC: Subconjunctival
*Control group was conjunctival autografting alone

achieving chemoreduction of OSSN, and a mean of 4 cycles (4 times daily with 7 days on and 7 days off) was able to reduce tumor burden by 57%. This approach made the subsequent resection of the tumor less challenging and simplified ocular surface reconstruction.[40]

Primary Acquired Melanosis and Melanoma

Primary acquired melanosis (PAM) with atypia is a melanocytic lesion of the conjunctival epithelium that may potentially evolve into melanoma,[41] and MMC has been utilized to treat this pathology. Treatment regimens have consisted of 0.04% MMC drops 4 times a day with 14-day cycles,[42] as well as 0.02% MMC 4 times a day for 2 weeks followed by 2 weeks of 0.04% MMC 4 times a day and ending with 3 months of 0.02% MMC twice a day.[43] Kurli et al.[44] reported using MMC both as an adjuvant to excision and cryotherapy or as primary treatment for PAM with atypia and conjunctival melanoma. The authors used 0.04% MMC 4 times a day, either for 28 days for primary treatment or 7 days when used as an adjuvant. In this study, the overall RR was 50% in both groups.[44] In addition, the authors reported a higher incidence of recurrence for multifocal tumors, among which 70% recurred.[44]

MMC employed to treat conjunctival melanoma appeared to be more effective when used as an adjuvant (50% RR) than primary treatment (100% RR).[44] Ditta et al.[45] described the use of MMC as an adjuvant for conjunctival melanoma with a treatment regimen of 3-week-long cycles of 0.04% MMC 4 times a day, separating cycles with 1 week of steroid drop use. Most patients (93%) underwent at least 3 cycles, and an overall recurrence of 33.3% was observed.[45] An observational case report documented the use of neoadjuvant 0.04% MMC 4 times a day for 3 weeks and post-excision adjuvant 0.04% MMC for another 4 cycles. This treatment approach was effective for the patient's conjunctival melanoma without any signs of recurrence after 32 months of follow-up.[46]

Photorefractive Keratectomy

Photorefractive keratectomy (PRK) is a surgical technique that uses an excimer laser to correct refractive error.[47] A common complication after PRK is the development of corneal haze due to aberrant corneal healing.[48] A recent meta-analysis of 3,536 eyes demonstrated that MMC helps reduce early and late-onset post-PRK haze.[49] A common protocol for MMC use in this application is intraoperative 0.02% MMC for 30 seconds, which has been primarily established for eyes with greater than 6 diopters (D) of myopia.[50] Virasch et al.[51] studied the relationship between MMC application time and the development of corneal haze and visual outcome. A concentration of 0.02% MMC was used for 12 seconds, 1 minute, or 2 minutes for eyes with a spherical equivalent of approximately -6.5 to -7.1 D of myopia. In this study, no difference was observed for haze scores or best-corrected visual acuity among the groups,[51] and shorter application times appeared to be as effective in haze prophylaxis as longer application times. Kaiserman et al.[52] analyzed the correlation between 0.02% MMC application time and corneal haze development in a retrospective study with 7,535 eyes. In the moderate myopia group, there was 0% incidence of haze in the group with application times ≥40 seconds versus 1.3% in the <40 seconds group (p=0.03).[52]

Thornton et al.[53] compared the use of 0.002% MMC and 0.02% MMC for application times of either 30 seconds or 2 minutes. In this study, 0.02% MMC had a higher efficacy in preventing postoperative haze than 0.002% MMC in cases of myopia ≥-6.00 D and ablation depths of ≥75 µm. In patients with lower degrees of myopia or ablation depths less than 75 µm, both concentrations appeared to be equally effective. This study also compared the degree of haze formation when applying 0.002% MMC for either 30 seconds or 2 minutes, but changing the exposure time did not appear to impact the degree of haze formation.[53] Shojaei et al.[54] used 0.02% MMC for 5 seconds in eyes undergoing PRK with ablation depths less than 65 µm and reported decreased haze formation in eyes receiving this treatment versus control eyes. At 6-month follow-up, 11.5% of control eyes had trace haze and 1.3% had 1+ haze, while 1.4% of treated eyes had trace haze and 0% had 1+ haze.[54] The findings from the studies above are summarized in Table 5.

Table 5. Use of mitomycin C (MMC) in photorefractive keratectomy

Concentration	Application time	Findings	Reference
0.02%	12 s	Short (12 s) and long (1-2 min) application times were equally effective in haze prophylaxis.	Virasch et al.[51]
	1 min		
	2 min		
0.02%	<40 s	Significantly higher incidence of haze formation in the shorter application time group (1.3% vs. 0%, p=0.03).	Kaiserman et al.[52]
	≥40 s		
0.002%	30 s	Different exposure times while using 0.002% MMC did not appear to impact the degree of haze formation.	Thornton et al.[53]
	2 min		
0.002%	30 s - 2 min	0.02% MMC was more effective than 0.002% MMC for haze prophylaxis in cases of myopia ≥-6.00 diopters and ablation depths of ≥75 µm. In cases involving less myopia or ablation depth, both concentrations were equally effective.	
0.02%			
0.02%	5 s	Trace haze occurred in 1.4% of treated eyes and 11.5% of untreated eyes. 1+ haze occurred in 0% of treated eyes and 1.3% of untreated eyes.	Shojaei et al.[54]

Phototherapeutic Keratectomy

Phototherapeutic keratectomy (PTK) is a surgical technique that utilizes an excimer laser to treat anterior stromal conditions.[55] Pathologies commonly treated with PTK include Reis-Bücklers dystrophy, granular dystrophy, macular dystrophy, Salzmann nodular degeneration, keratoconus nodules, and anterior stromal scars.[56] One of the main potential limitations of PTK is recurrence of the original pathology,[57] and MMC has been used in conjunction with PTK to decrease or delay recurrence.

PTK alone is associated with clinically significant RRs of 47% of eyes with Reis-Bücklers dystrophy, 23% of eyes with granular corneal dystrophy, 14% of eyes with lattice dystrophy, 14% of eyes with macular corneal dystrophy, and 15% of eyes with Salzmann nodular degeneration.[57,58,59] Due to the high recurrence of these corneal pathologies, PTK with the additional use of MMC has been employed.

Granular dystrophy and macular dystrophy have been treated with regimens consisting of PTK and MMC 0.02% for 30 seconds, after which significant recurrences occurred in 11.1% of treated patients in each group.[60] Reis-Bücklers dystrophy has been treated with 0.02% MMC for 2 minutes, and in a case report, this regimen resulted in no recurrence at 1-year follow-up.[61] Salzmann nodular degeneration has been treated with PTK and 0.02% MMC for 1-2 minutes to prevent recurrence and improve visual symptoms, mainly contrast sensitivity and higher-order corneal aberrations.[62,63] Reddy et al.[62] reported using 0.02% MMC for 60 seconds on 13 eyes with Salzmann nodules, none of which recurred in a follow-up time of 3 months. Avellino dystrophy has been treated with PTK and 0.02% MMC for 2 minutes. Kim et al.[64] reported on 4 patients treated with this approach. Two patients were homozygous for the Avellino corneal dystrophy mutation in the *BIGH3* gene, and both of them had a recurrence. However, the remaining 2 patients were heterozygous and showed no signs of recurrence.

Epithelial Ingrowth

Epithelial ingrowth is an uncommon complication of LASIK surgery in which epithelial cells proliferate between the LASIK flap and underlying stromal bed.[65] Wilde et al.[66] reported positive outcomes when using MMC to treat recalcitrant epithelial ingrowth in post-LASIK eyes. Four eyes were treated with 70% alcohol followed by 0.02% MMC, both on the stromal bed and under the flaps, after mechanical debridement of the epithelial ingrowth. The flap was then secured in place using fibrin glue. For all eyes, visual acuity improved and no recurrence was observed.[66] Taneri et al.[67] reported a case of a buttonholed LASIK flap that developed epithelial ingrowth. In this case, PTK was performed with application of 0.02% MMC on the corneal stroma for 1 minute. After treatment, no recurrence was seen.[67] In another case, severe post-LASIK epithelial ingrowth was treated with flap amputation followed by PTK and 0.02% MMC for 2 minutes. In this case, overall visual acuity improved and no complications were seen.[68] In all these reports it is unclear how much the MMC affected the recurrence of the epithelial ingrowth, but it most likely decreased the subsequent corneal haze or scarring.

Epithelial Downgrowth

Epithelial downgrowth is a complication of ocular trauma or surgery in which epithelial cells enter the anterior chamber and proliferate over intraocular tissue.[69] MMC has been used to treat cystic epithelial downgrowth following cataract surgery. Yu et al.[70] reported a case where cystic fluid from the epithelial downgrowth was aspirated, then a solution of 0.0002 mg/mL of MMC was injected into the lesion and left there for 5 minutes, after which the MMC was washed out of the cyst with balanced salt solution. The cyst decreased in size and vision improved, but the authors noted that this procedure should be performed with great care due to high-risk complications if MMC were to leak into the anterior chamber.[70]

Other Applications of MMC in Ocular Diseases

The use of MMC has been shown to increase the success rate of filtering procedures for the treatment of glaucoma. It is currently used in trabeculectomy, bleb needling, and ab-interno filtering procedures.[71] MMC at 0.02% has also proven useful when performing a dacryocystorhinostomy as it can prevent the development of scar tissue by decreasing the contraction and migration of fibroblasts that occurs in response to injury. Additionally, it seems to reduce the osteotomy closure rate.[72,73] In the case of strabismus surgery, MMC appears to decrease the formation of postoperative adhesions.[74,75]

Toxicities and Potential Complications of MMC

Although MMC has shown promising results in treating ocular disease, there are a variety of potential complications to consider. In pterygium surgery, complications reported include: corneal edema, corneal perforation, scleral stromal necrosis with possible infectious scleritis, secondary glaucoma, corectopia, iritis, cataract, and endophthalmitis.[76,77,78,79,80,81] Safianik et al.[79] documented two cases of scleral melt and one case of limbal perforation with iris incarceration after using 0.02% MMC for 3 minutes for pterygium surgery. These patients ultimately required a tectonic graft in the case of the limbal perforation, and conjunctival grafts for the scleral melts. Rubinfeld et al.[78] documented the possible complication of developing secondary iritis after pterygium surgery with postoperative 0.04% MMC drops 4 times a day. In another case in this series, a patient developed a scleral melt that led to a peaked pupil toward the side of the lesion.[78] Importantly, MMC has been associated with scleral necrosis decades after exposure, and therefore continued and regular follow-up of these patients is necessary.

MMC use in ocular surface surgeries has also been associated with endothelial cell loss. Bahar et al.[77] reported that employing intraoperative 0.02% MMC for 2 minutes in pterygium surgery resulted in an endothelial cell loss of 6% at 1 month after surgery, while no significant endothelial cell loss occurred in the control group. Avisar et al.[76] reported that employing 0.02% MMC for 5 minutes during pterygium surgery can lead to endothelial cell loss of 21.05%±3.2% at 3 months after surgery. In the case of epithelial downgrowth, Yu et al.[70]

reported a 13.3% decrease in endothelial cell density following the use of 0.0002 mg/mL MMC for 5 minutes. MMC usage in PRK has also been linked to endothelial cell loss. Some studies have reported that employing 0.02% MMC for 10-50 seconds correlated to a statistically significant decrease in endothelial cells compared to PRK alone.[82,83] However, the vast majority of studies regarding this potential toxicity report no statistically significant change in endothelial cell density when employing MMC with PRK.[54,84,85,86,87,88,89] Even studies with a larger number of subjects and longer follow-up periods did not find any correlation, suggesting a favorable safety profile with minimal, if any, risk of endothelial cell loss when employing MMC with PRK.[84,85]

Endophthalmitis after pterygium surgery with MMC is very rare. Peponis et al.[81] published a case report of a patient who developed endophthalmitis following the use of 0.02% MMC for 1 minute. In this case, the subject had a scleral melt 21 days after surgery with fungal endophthalmitis (*Fusarium* species). The patient was treated with antibiotics and antifungals, vitrectomy, scleral patch, tectonic graft, and finally enucleation.[81] Yi et al.[90] presented another case in which the subject developed endophthalmitis with *Serratia marcescens* which was treated with vitrectomy and antibiotics. This treatment led to the resolution of the infection, but the patient developed significant vision loss. The authors suggested that the impaired scleral barrier after surgery with MMC and the patient's immunosuppressed state may have played a role in the infectious process.[90]

MMC use in the other aforementioned applications has a less severe complication profile. MMC employed for OSSN has a risk of allergic reaction, epithelial surface toxicity, punctal stenosis, and limbal stem cell deficiency. These are managed with topical steroids, artificial tears, and punctal plugs.[91] Conjunctival hyperemia and lacrimation are well documented, in addition to delayed epithelial healing.[92,93] MMC use for PAM and melanoma may lead to keratoconjunctivitis, corneal abrasion, pannus, and corneal haze.[44] To minimize the risk of complications as a result of MMC, it may be beneficial to limit exposure times and use lower concentrations.[10,19,20]

Conclusion

MMC has demonstrated high utility in a wide array of ocular pathologies, especially in the field of cornea and external disease, due to its ability to alter tissue remodeling. Currently, there is a need to further establish the optimum treatment protocols for each aforementioned indication. Although MMC usage has promising results, it could lead to potentially vision-threatening complications, and judicious use is therefore warranted.

Ethics

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Concept: M.A.C., C.J.R., Z.A.S., Design: M.A.C., C.J.R., Z.A.S., Data Collection or Processing: M.A.C., C.J.R., Z.A.S., Analysis or Interpretation: M.A.C., C.J.R., Z.A.S., Literature Search: M.A.C., C.J.R., Z.A.S., Writing: M.A.C., C.J.R., Z.A.S.

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Case Report

Lamellar Keratoplasty Using Microkeratome-Assisted Anterior Lamellar Graft in the Management of Deep Limbal Dermoid: A Case Report

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Abstract

Limbal dermoid is a congenital benign tumor of the limbus which is often managed by surgery if necessary. In dermoid lesions involving the deep stroma, tumor excision and reconstruction of the anterior segment with amniotic membrane transplantation or keratoplasty may be required. Herein, we present a case of deep limbal dermoid treated with surgical resection and lamellar keratoplasty using microkeratome-assisted anterior lamellar graft.

Keywords: Limbal dermoid, excision, microkeratome-assisted anterior lamellar graft, lamellar keratoplasty, reconstruction

Introduction

Limbal dermoid is a congenital benign tumor of the limbus. It accounts for 10% of all and 29% of benign limbal tumors.[1,2] Anatomically, limbal dermoids are classified into three groups according to the depth of invasion of the anterior segment components. Grade I tumors are superficial lesions, grade II tumors involve part of the corneal stroma, and grade III tumors occupy the full corneal thickness and may penetrate into the anterior chamber.[3] Surgical removal is often opted for grade II and III lesions. The choice of surgery can be simple excision, or anterior segment reconstruction via amniotic membrane transplantation (AMT) with or without autologous limbal stem cell transplantation, or lamellar keratoplasty.[4,5,6,7,8] Penetrating keratoplasty is usually opted for lesions involving the full thickness of the cornea or in case of corneal perforation during excision.[8] Herein, we present a case of grade II limbal dermoid treated with lamellar excision and lamellar keratoplasty via microkeratome-assisted anterior lamellar graft.

Case Report

A 2.5-year-old boy was referred to our clinic with the diagnosis of limbal dermoid in the left eye leading to progressively increasing astigmatism. Visual acuity (VA) of the left eye was 20/200. Clinical examination revealed a corneal-conjunctival fleshy dome-shaped lesion measuring approximately 8.5x8.5 mm in size. The visual axis was partially occluded by the lesion (Figure 1). Refractive error could not be measured accurately due to distortion of the retinal reflex on retinoscopy. The patient had no history of associated systemic abnormality.

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The lesion was removed from the corneal surface manually using a 57 Beaver knife. After excision, the remaining stroma appeared very thin, and no thickness measurement could be done with an ultrasound pachymeter. A lamellar corneal button 0.5 mm larger than the excised dermoid bed was fashioned using the automated lamellar keratoplasty technique. The donor tissue was placed on an artificial anterior chamber and after removal of the epithelium, a 9-mm corneal flap 300 µm in thickness was obtained using a Moria microkeratome (Moria Inc., Doylestown, PA, USA). This tissue was then placed to cover the excised area on the cornea and sclera, and was sutured to the surrounding tissues with interrupted 10/0 monofilament nylon sutures (Ethilon 10.0, Ethicon, Johnson & Johnson, USA). Postoperatively, a bandage contact lens (AirOptix Night & Day, Alcon, USA) was placed on the eye and the patient was prescribed topical prednisolone acetate 1% (PredForte, Allergan Pharmaceuticals, Ireland) and fluoroquinolone 0.5% eye drops (Vigamox, Alcon, USA) 4 times a day for 1 week. One week later, prednisolone acetate drops were replaced by loteprednol etabonate 0.5% (Lotemax, Bausch & Lomb, USA) 4 times a day for 1 week. One week later, prednisolone acetate drops were replaced by loteprednol etabonate 0.5% 4 times a day and the steroid dose was gradually tapered at follow-up examinations over a period of 3 months. Occlusion of the right eye was started for the treatment of amblyopia. The corneal sutures were removed at postoperative 3 months. One year after the surgery, the lamellar graft looked healthy with no epithelial defect, corneal vascularization, or inflammation. Mild stromal haze was noted (Figures 2a, 2b). Uncorrected VA was 40/200 and cycloplegic retinoscopy revealed refraction values of +2.75 D sphere and +1.00 D cylinder with a 70° axis.

Discussion

After excision of deep limbal dermoids, leaving bare stroma is usually not recommended due to the postoperative tendency towards the formation of scar tissue, neovascularization, and pseudopterygium. Various methods of reconstruction to decrease the scarring and pseudopterygium have been reported, including the use of mitomycin C after excision, AMT with or without limbal stem cell transplant, or lamellar keratoplasty with lamellar/full-thickness grafts.[4,5,6,7,8]

Full-thickness grafts for lamellar keratoplasty may be more prone to complications such as prolonged reepithelization, interface neovascularization, steroid-induced glaucoma, and graft rejection.[9] Lamellar keratoplasty with lamellar grafts is more commonly used with complications including mild interface haze and pseudopterygium.[7,8] Varying degrees of astigmatism can occur as a result of increased length of cornea invaded by the limbal dermoid.[10]

Automated lamellar therapeutic keratoplasty is a relatively new technique which was developed to obtain better postoperative anatomic and refractive outcomes. In this technique, the diseased portion of the stroma is removed using a microkeratome with adjustable heads. Then, a matching lamella of stroma is obtained from the donor tissue with the aid of an artificial anterior chamber and microkeratome. One of the advantages of using microkeratome heads to prepare an anterior lamellar graft is the ease of obtaining a flap, which decreases the duration of the surgery and facilitates reproducible results.[11] It is also reported to have better outcomes than manual lamellar keratoplasty in terms of surface epithelization and postoperative refraction since it forms a smooth graft which is in optimal alignment with the host tissue.[11,12] Our patient demonstrated a healthy donor cornea with no epithelial defect, and mild astigmatism at the end of follow-up. Although the donor-host tissue apposition was not perfect because of manual excision of the dermoid, a smoother and more regular donor flap could be obtained with the automated technique, which probably contributed to faster epithelization and a more regular surface leading to mild astigmatism.

Anterior segment optical coherence tomography (OCT) and/or ultrasound biomicroscopy may be useful tools to evaluate the depth of tumor invasion, estimate the thickness of the tissue to be excised, and better follow up the donor-recipient tissue interface.[13,14] These these measurements could not be performed in our case due to the young age of the patient. Intraoperative

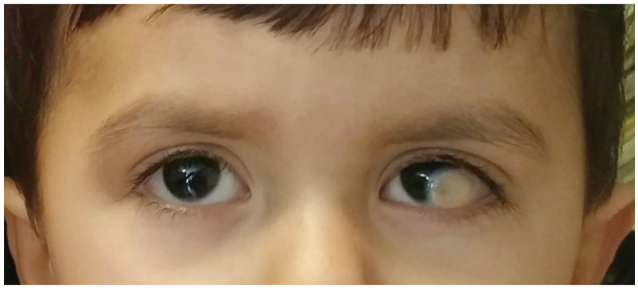

Figure 1. Preoperative picture of left eye limbal dermoid occluding the visual axis

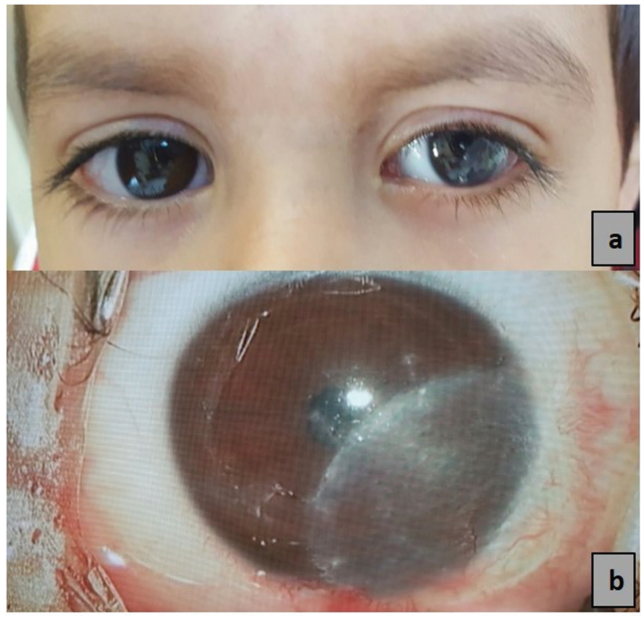

Figure 2. One-year postoperative picture with no epithelial defect or neovascularization. Mild stromal haze is observed

OCT can also be utilized during excision to help achieve a smooth ocular surface free of lesion.[15]

In conclusion, microkeratome-assisted anterior lamellar grafts can be used for ocular surface reconstruction following the excision of deep/large dermoids. This approach provides better wound healing and the remaining tissue can be used for endothelial keratoplasty.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: Ö.Ö.U.G., A.K.G., H.N.B., Design: Ö.Ö.U.G., A.K.G., H.N.B., Data Collection or Processing: Ö.Ö.U.G., A.K.G., H.N.B., Analysis or Interpretation: Ö.Ö.U.G., A.K.G., H.N.B., Literature Search: Ö.Ö.U.G., A.K.G., H.N.B., Writing: Ö.Ö.U.G., A.K.G., H.N.B.

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Case Report

A Case of Concurrent Acute Macular Neuroretinopathy and Paracentral Acute Middle Maculopathy Following Pfizer-BioNTech COVID-19 Vaccination

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Abstract

We present a 65-year-old woman who developed sudden and severe vision loss in her left eye one day after the administration of the second dose of COVID vaccine. The best corrected visual acuity in this eye was 1/10. Diffuse paracentral acute middle maculopathy was detected on spectral domain optical coherence tomography (OCT). OCT angiography images revealed concurrent vascular flow defects consistent with acute macular neuroretinopathy in the deep retinal capillary plexus and choriocapillaris layers. At the end of the six-month follow-up, there was no improvement in visual acuity, and atrophy and thinning developed in all layers of the retina.

Keywords: Acute macular neuroretinopathy, optical coherence tomography angiography, paracentral acute middle maculopathy, Pfizer-BioNTech COVID-19 vaccine, spectral domain optical coherence tomography

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Introduction

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused the coronavirus disease (COVID-19) pandemic, has caused many deaths and serious morbidity worldwide. In the last months of 2020, the US Food and Drug Administration (FDA) issued emergency use permits for some vaccines, and accelerated vaccine campaigns were launched in many countries. Following the widespread administration of COVID-19 vaccines produced using different technologies, reports also emerged of various vaccine-related systemic and ocular adverse effects.[1,2,3,4]

There are a few cases in the literature related to the retinal complications of vaccines. Among these, cases of acute macular neuroretinopathy (AMN), paracentral acute middle maculopathy (PAMM), and retinal artery and vein occlusions are most common, and most occurred after the administration of inactivated virus and adenovirus-vector COVID-19 vaccines, with fewer cases observed in association with messenger RNA (mRNA) vaccines.[1,2,3,4,5,6,7,8]

First described as a variant of AMN (type I AMN) by Sarraf et al.[9] in 2013, PAMM is a retinal finding characterized by sudden-onset paracentral scotomas and a focal or diffuse hyperreflective band-like lesion in the inner nuclear layer (INL) and inner plexiform layer (IPL) above the outer plexiform layer (OPL) on spectral domain optical coherence tomography (SD-OCT). Although it may be idiopathic, it has often been reported to develop secondary to retinal vascular diseases such as diabetic and hypertensive retinopathy, retinal artery and vein occlusion, or a systemic disease, and ischemia in the middle and/or deep retinal capillary plexus has been implicated in its pathogenesis.[9,10,11,12]

To the best of our knowledge, this article is the first published report of a case of AMN and concomitant PAMM presenting with sudden and severe vision loss and in one eye immediately after Pfizer-BioNTech COVID-19 vaccination, with multimodal imaging features including optical coherence tomography angiography (OCTA).

Case Report

A 65-year-old female medical doctor presented with complaints of sudden-onset central vision loss and blotchy vision in her left eye starting 4 hours earlier. The patient reported receiving a second dose of the Pfizer-BioNTech vaccine the day before, the first dose of Pfizer-BioNTech vaccine 3 months before this vaccine, and two Synovac vaccines 6 and 8 months earlier. She had a history of drug-controlled diabetes mellitus, stage 1 hypertension, stage 1 chronic kidney disease, alcohol drinking habit, and low water intake.

Her best corrected visual acuity (BCVA) was 10/10 in the right eye and 1/10 in the left eye (with head movement), and intraocular pressure (IOP) was 12 mmHg in both eyes. On slit-lamp examination, the anterior segment and fundus of both eyes appeared normal.

On infrared (IR) imaging of the left eye, there was a lobular-appearing hyporeflective lesion in the parafoveal area that covered the entire macula (Figure 1A). Short-wavelength (488 nm) blue fundus autofluorescence (FAF) imaging also revealed lobular, markedly hypoautofluorescent areas in the left eye corresponding to the lesion area in IR images (Figure 1B). On fluorescein angiography (FA), all phases and filling times were normal in the left eye (Figure 1C, D). On SD-OCT of the left eye, a diffuse band of hyperreflectivity and thickening in the INL and IPL above the OPL was detected in the parafoveal area and was more pronounced on the nasal side. A band of hyporeflectivity and granular appearance were also detected just below these areas in the outer nuclear layer (ONL), external limiting membrane (ELM), and ellipsoid zone (EZ). In the INL, 1-2 small intraretinal cysts were observed (Figure 1E). In the en face OCTA images, the foveal avascular zone in the left eye was noted to be irregular and slightly enlarged (Figure 1F) and there were concurrent marked vascular flow defects in the deep retinal capillary plexus and choriocapillaris (Figure 2A, B). The areas of flow defect were consistent with the lesion areas seen in IR and FAF. In addition, there was a marked decrease in vascular density and increased retinal thickness in the deep retinal capillary plexus in the parafoveal region on OCTA (Figure 2C).

Although IR, FAF, FA, OCT, and en face OCTA imaging in the right eye (Figure 3A, B, C, D, E, F) were completely normal, small vascular flow defects were observed in the deep retinal capillary plexus on OCTA, while no flow defects were detected in the coriocapillaris and vascular density was found to be normal in the deep retinal layers (Figure 4A, B, C).

The presumed diagnosis for the left eye was diffuse PAMM with microvascular obstructions in the capillary beds of the deep retinal layers and choriocapillaris associated with the Pfizer-BioNTech vaccine. Treatment was initiated with an IOP-lowering agent (timolol-dorzolamide combination eye drops twice daily; Tomec drops, Abdi İbrahim Pharmaceuticals, Istanbul, Turkey), an antiaggregant (acetylsalicylic acid 100 mg/day; Coraspin tablet, Bayer Türk Chemical Co., Istanbul, Turkey), a vasodilator (pentoxifylline 400 mg twice daily; Trental tablet, Sanofi Health Products Ltd. Sti., Istanbul, Turkey), a corticosteroid (prednisolone 32 mg/day; Prednol tablet, Mustafa Nevzat Pharmaceuticals, Istanbul, Turkey), and vitamin C (500 mg/day), and ample fluid consumption was recommended. Consultations with the infectious diseases, cardiology, hematology, nephrology, and genetics units, thrombophilia panel, hemogram and D-dimer tests, and carotid Doppler ultrasonography were requested as etiological studies. As a result of all examinations, it was determined that the patient's comorbidities were under control and she had no genetic predisposition to thrombophilia.

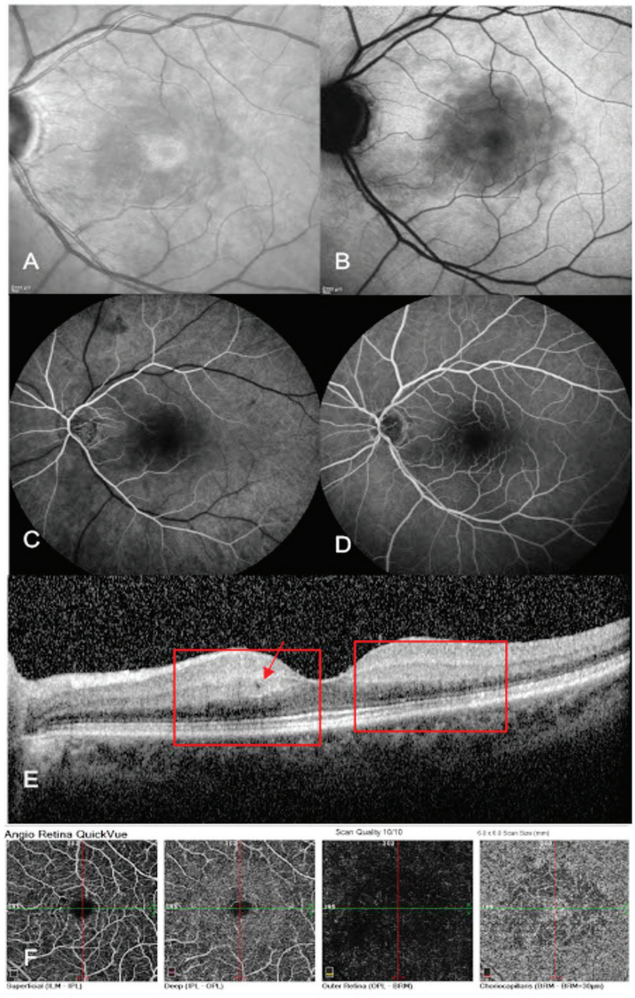

Figure 1. Left eye, initial examination. A) Infrared photography; B) fundus autofluorescence; C,D) fluorescein angiography, early and late phase; E) spectral domain optical coherence tomography showing diffuse hyperreflectivity and thickening of the inner plexiform and inner nuclear layers and hyporeflectivity and granular appearance in the outer retinal layers (red square) with a cyst in the inner nuclear layer (red arrow); F) en face optical coherence tomography angiography

The patient was followed up weekly at first and later at 15-day and 30-day intervals for 6 months.

At 6-month follow-up, BCVA was still 1/10 in the left eye, IR and FAF images were normal, collateral vessels had formed in the optic nerve head, and FA demonstrated filling of these vessels in the arterial phase, with no leakage (Figure 5A-D). In the SD-OCT examination, in addition to atrophy and thinning in all retinal layers, the hyporeflective and granular appearance in the ELM and EZ persisted in the parafoveal area (Figure 5E). On OCTA imaging, the flow defects in the choriocapillaris had resolved while those in the deep retinal capillary plexus persisted (Figure 5F, 6A, B, C).

Discussion

To the best of our knowledge, this article is the first published report of a case of AMN presenting with sudden and severe vision loss and concomitant diffuse PAMM with vascular flow defects in the deep retinal capillary plexus in one eye immediately after receiving the Pfizer-BioNTech recombinant mRNA COVID-19 vaccine, with a description of multimodal imaging features including OCTA.

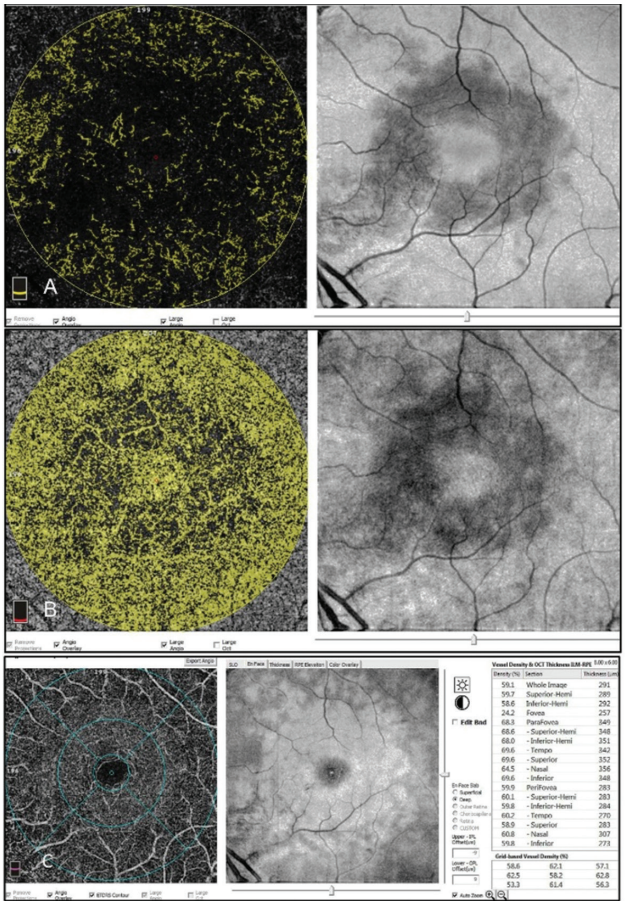

Figure 2. Left eye, optical coherence tomography angiography at initial examination. A) deep retinal capillary plexus vascular flow defects; B) choriocapillaris vascular flow defects; C) deep retinal capillary plexus vascular density changes

Although many instances of PAMM and AMN after receiving inactivated virus and adenovirus-vector COVID-19 vaccines have been documented in the literature, only one case of PAMM and two cases of AMN after the Pfizer-BioNTech COVID-19 vaccine have been described.[1-8] There is no report of AMN and PAMM developing concomitantly in the same eye. In a case of PAMM described by Ishibishi et al.,[6] complaints occurred on day 7 after the second dose of Pfizer-BioNTech vaccine, visual acuity was perfect, the lesion was focal, and OCTA imaging was not performed. Similarly, AMN cases reported in association with the Pfizer-BioNTech vaccine appeared on days 2 and 8 after the second dose of vaccine, visual acuities were well preserved, and lesions were focal.[1,6]

Although PAMM and AMN are regarded as two distinct clinical entities both characterized by sudden-onset paracentral

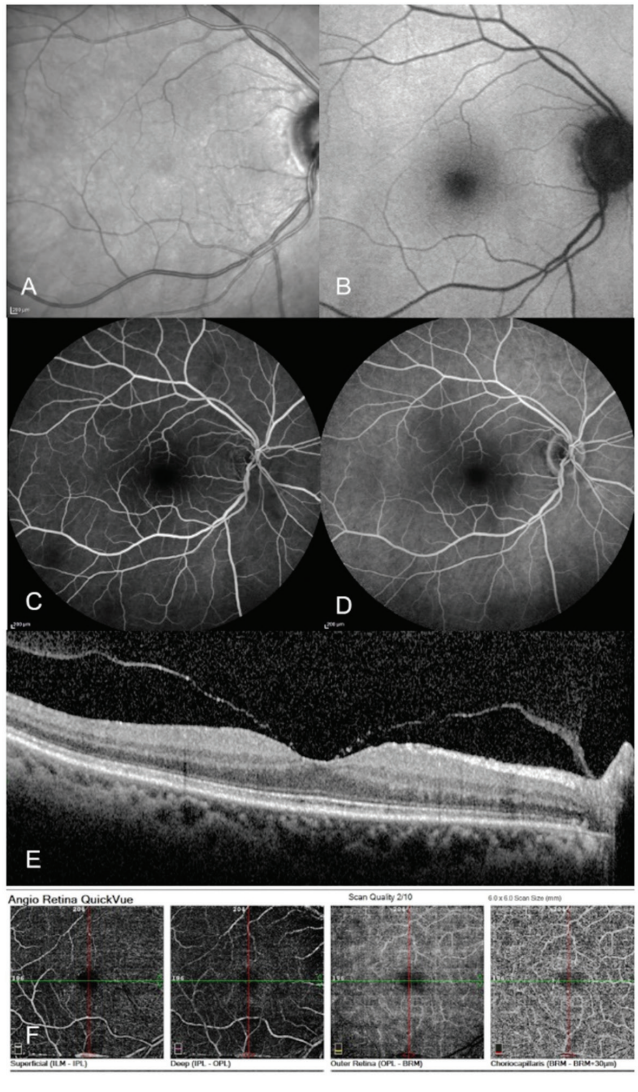

Figure 3. Right eye, initial examination. A) infrared photography; B) fundus autofluorescence; C,D) fluorescein angiography, early and late phase; E) spectral domain optical coherence tomography; F) en face optical coherence tomography angiography

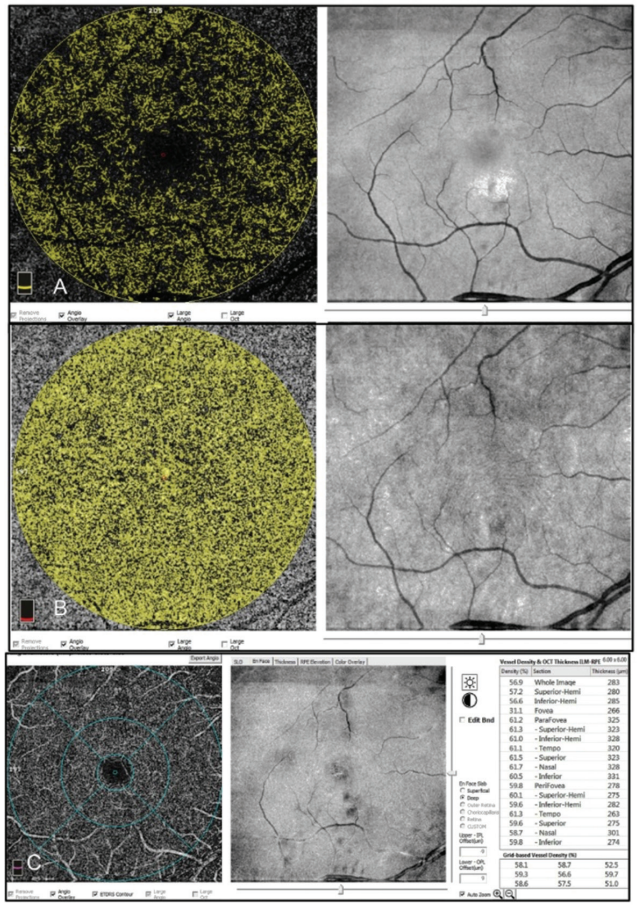

Figure 4. Right eye, optical coherence tomography angiography at initial examination. A) deep retinal capillary plexus vascular flow; B) choriocapillaris vascular flow; C) deep retinal capillary plexus vascular density

scotomas and hyporeflective paracentral lesions on IR imaging, Sarraf et al.[9] reported in 2013 that there were actually two variants of AMN, PAMM being one of them, and they named PAMM "type I AMN." They named the other variant, in which only the outer retinal layers (i.e., the ONL and EZ) are affected, type II AMN. To date, a case of AMN and PAMM occurring simultaneously in the same eye has not been described in the literature. Therefore, we think that our case could be defined as a new variant, type III AMN (combined AMN), in addition to the type I and II AMN variants defined by Sarraf et al.[9]

Our case was accompanied by sudden and severe vision loss, and SD-OCT imaging demonstrated PAMM as a diffuse hyperreflective band appearing on both sides of the central macula. In the literature, it has been emphasized that if PAMM is diffuse, it may be a symptom of latent or reperfused central retinal artery occlusion (CRAO).[10,12,13] However, the absence of signs consistent with CRAO on fundus examination or SD-OCT imaging, the normality of arterial filling time as well as all phases and the peripheral retina on FA, and the presence of vascular flow defects in the choriocapillaris, which has a different circulatory supply, were data that led us away from a diagnosis of latent or reperfused CRAO in our case.

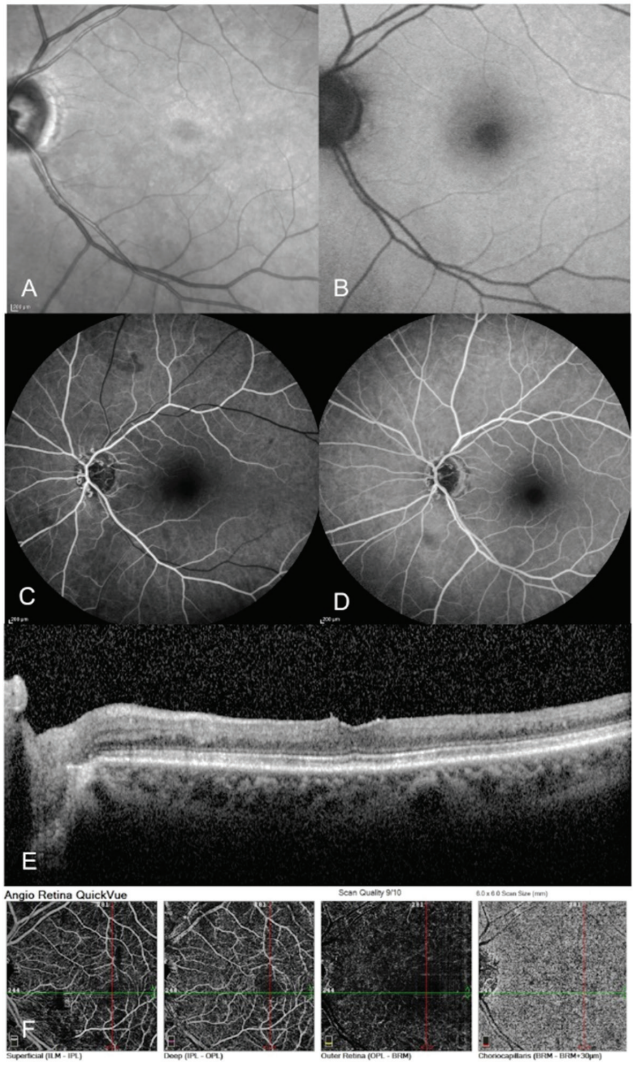

Figure 5. Left eye, 6 months later. A) infrared photography; B) fundus autofluorescence; C,D) fluorescein angiography, early and late phase; E) spectral domain optical coherence tomography; F) en face optical coherence tomography angiography

The SD-OCT images of our patient showed a hyporeflective and granular appearance in the outer retinal layers in the parafoveal region just below the PAMM lesions. Sarraf et al.[9] reported that in PAMM (i.e., type I AMN), hyperreflectivity in the middle layers may be associated with a corresponding finding in the outer retinal layers, which they attributed to a shadowing effect. However, in our patient's 6-month SD-OCT images, the PAMM-related hyperreflectivity had resolved and the entire retina was atrophic and thinned, but the hyporeflective and granular appearance in the outer retinal layers persisted. This cannot be explained by the shadowing effect, thus leading us to believe the appearance of the outer retinal layers was a sign of disease involvement in these layers.

OCTA is a new, non-invasive, and reproducible imaging technique that enables evaluation of the vascular structures of the

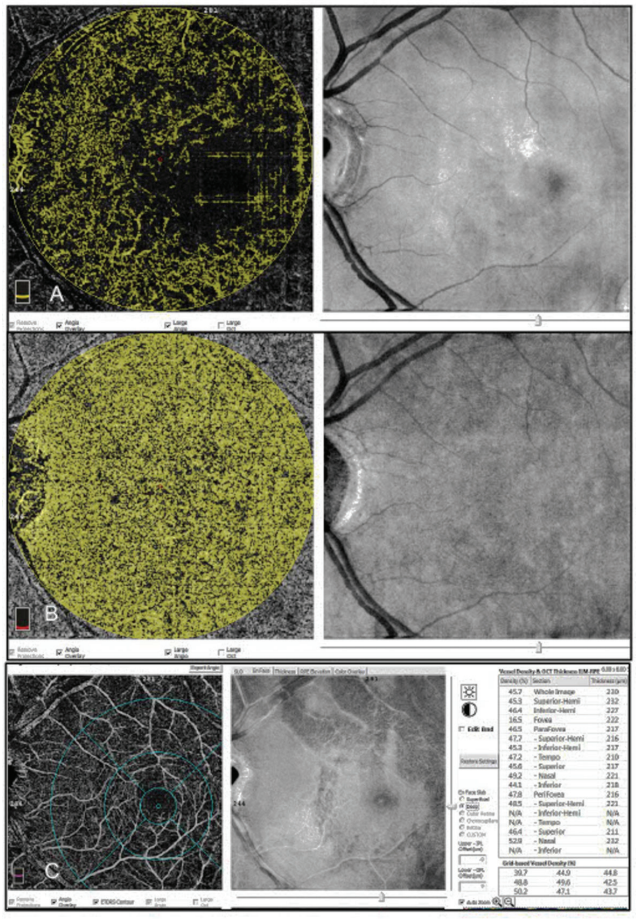

Figure 6. Left eye, optical coherence tomography angiography at 6-month follow-up. A) deep retinal capillary plexus vascular flow defects; B) choriocapillaris vascular flow defects; C) deep retinal capillary plexus vascular density changes

retina and choriocapillaris. It also aids in accurately determining the presence of local ischemia by measuring vessel density. En face OCTA imaging of our patient revealed enlargement of the foveal avascular zone and significant vascular flow defects in both the deep capillary plexus of the retina and the choriocapillaris. Concomitant flow defects in the choriocapillaris layer, which has a completely different circulatory supply than the retina, suggests a condition that affects the entire capillary vascular system. In recent years, OCTA has been used to investigate the presence and extent of flow defects in the retinal capillaries and choriocapillaris in patients with PAMM and AMN. Chu et al.[11] detected microvascular changes in the form of attenuated flow signals on OCTA in the middle and deep retinal capillary plexus in eyes with PAMM and in the deep retinal capillary plexus in eyes with AMN. Another study by Casalino et al.[14] demonstrated defects in both the deep retinal capillary plexus and the inner choroidal vascular plexus on OCTA in eyes with AMN affecting the outer retinal layers. In their OCTA studies, Lee et al.[15] and Hwang and Sen[16] observed concurrent vascular flow defects in both the deep retinal capillary plexus and the choriocapillaris in OCTA images of AMN patients exhibiting outer retinal layer involvement on SD-OCT. Based on these findings, they argued that concurrent vascular defects in two independent vascular plexuses suggests the coexistence of both vascular and inflammatory etiologies in the pathogenesis of AMN.

Vaccines are one of the most effective ways to prevent infections. Over the last decade, mRNA technology has become a promising tool in vaccine development. These types of vaccines are mainly designed for cancer immunotherapy and prevention of infectious diseases, and are characteristically very stable. Spike antigens are encapsulated and have been shown in several clinical trials to have very good efficacy and safety profiles.[4,17] However, it is also known that all vaccines can lead to various undesirable immunological events by causing abnormal activation of the innate and acquired immune system. Inflammation due to such immunological events can result from a component of the vaccine, a hypersensitivity reaction, or autoimmunity, as well as from the virus spike antigen, human adenovirus, or other viral antigens.[18]

We believe that our patient had a new AMN variant, type III (combined) AMN. The presence of diffuse PAMM in SD-OCT images was consisten with type I AMN, while the concurrent vascular flow defects in both the deep retinal capillary plexus and choriocapillaris on OCTA imaging were regarded as findings consistent with type II AMN. Due to the development of concurrent microvascular occlusions in capillary systems with different circulatory sources such as the retina and choroid, we think that the pathogenesis involved an immune response to virus antigens (i.e., inflammation associated with an antigen-antibody reaction) affecting the capillary vascular endothelium, as previously described in people infected with COVID-19.[19]

Ethics

Peer-review: Externally peer reviewed.

Authorship Contributions

Data Collection or Processing: S.N., C.D., Literature Search: S.N., Writing: J.M.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

Late-Onset Neuromyelitis Optica Spectrum Disorder Mimicking a Non-Arteritic Anterior Ischemic Optic Neuropathy–Case Report

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Abstract

A 60-year-old white woman presented to the emergency department with painless decrease of visual acuity in the left eye (LE). The diagnosis of a non-arteritic anterior ischemic optic neuropathy in the LE was established based on the clinical picture and the results of static perimetry, fluorescein angiography, visual evoked potential, and magnetic resonance imaging (MRI) of the brain and orbit. Six months later, the patient reported visual impairment in the right eye (RE). Best corrected visual acuity (BCVA) in the RE was 5/10. Gadolinium-enhanced MRI showing inflammation of both optic nerves and the optic chiasm in correlation with positivity for immunglobulin G antibody against aquaporin-4 led to the diagnosis of late-onset neuromyelitis optica spectrum disorder. High-dose intravenous methylprednisolone therapy followed by oral tapering was administered and oral azathioprine was started to reduce the risk of further relapse. At discharge, BCVA was 5/5 in the RE. The patient remains under the care of neurology and ophthalmology clinics, with no recurrences for two years. The possibility of neuromyelitis optica spectrum disorder with optic neuritis in older patients is important in the differential diagnosis of ischemic optic neuropathy.

Keywords: Neuromyelitis optica spectrum disorder, late-onset NMOSD, optic neuritis, anti-aquaporin 4 antibody, AQP4

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a complex immune-mediated disease in which demyelination and loss of astrocytes constitute the main pathological findings in the central nervous system (CNS). It can affect the optic nerves, brain, brainstem, and spinal cord. The most common presentations are severe, recurrent attacks of optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM), distinct from multiple sclerosis (MS). Serological positivity for immunglobulin (Ig) G antibody against aquaporin 4 (AQP4) was found to be the pathologic cause as well as a reliable biomarker for NMOSD.[1,2]

The reported incidence of NMOSD ranges from 0.05 to 0.4 per 100,000 individuals.[2,3] However, these data are limited, as up to 29% of cases are initially misdiagnosed as MS.[3] Typical age at presentation is between 32 to 41 years, with a female predominance (woman constituting 70-90% patients with NMOSD).[2,3] It is postulated that there is also predilection for the non-white population, mainly people of East Asian and Afro-Caribbean descent.[4] NMOSD with onset at age ≥50 years is known as late-onset NMOSD (LO-NMOSD). It is an exceedingly rare presentation associated with worse final visual outcome, greater susceptibility to disability, and higher mortality rate.[5,6,7]

Case Report

A 60-year-old white woman presented to the emergency department with complaints of sudden, painless decreased visual acuity in the left eye (LE) for 3 days. There was no history of preceding trauma, eye drop usage, or ocular surgery. Systemic history included well-controlled hypertension and

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hypothyroidism. Best corrected visual acuity (BCVA) was 5/5 in the right eye (RE) and 5/10 in the LE. There was no pain associated with eye movements. Left relative afferent pupillary defect was present. Fundus examination revealed diffuse optic edema in the LE, while the right optic disc appeared normal but with no cup. Intraocular pressure was 18 mmHg in the RE and 19 mmHg in the LE.

The patient was admitted to the ophthalmology department for further work-up. Various tests including full blood count, prothrombin time, activated partial thromboplastin time, serum electrolytes, glucose level, C-reactive protein, serum erythrocyte sedimentation rate, renal, liver, and thyroid function tests, serum vitamin B_{12} and folate levels, angiotensin-converting enzyme, rheumatoid factor, antinuclear-antibody, anti-neutrophil cytoplasmatic antibody, double-stranded DNA, and anti-cardiolipin antibodies were within normal limits. Serological infective screening including anti-herpes simplex virus, *Borrelia burgdorferi* antibodies, hepatitis B surface antigen, anti-hepatitis C virus, Human Immunodeficiency Virus antibody/antigen combo, and treponemal antibody test for syphilis were all non-reactive. Deviations from the standard included elevated levels of total cholesterol (246 mg/dL, normal: 115-190), low-density lipoprotein cholesterol (164 mg/dL, normal: <115), and a history of cytomegalovirus infection (IgG 376 AU/mL, normal: <6.0; IgM 0.08 AU/mL, normal: <0.85). No abnormalities were detected on neurology and internal medicine consultations. Blood pressure was 110/75 mmHg. Magnetic resonance imaging (MRI) of the brain and orbit showed no abnormalities. However, the patient only agreed to undergo the examination without any contrast agent. She stated that she probably had an anaphylactic reaction to contrast in the past, but she was unable to accurately describe the incident and had no documentation.

Static perimetry in the LE demonstrated an inferior altitudinal defect in the visual field (VF) (Figure 1A). Fluorescein angiography (FA) in the LE showed increasing hyperfluorescence of the temporal part of the optic disc, with contrast leakage indicative of edema. Visual evoked potential (VEP) was normal in the RE, while the LE exhibited increased P100 latency (prolonged to 120%), an amplitude of 25% after 1° stimulation, and residual response after 15 minutes (Figure 2A, B). It was considered that these results may correspond to a non-arteritic anterior ischemic optic neuropathy (NAION) in the LE.

During hospitalization, the patient received topical brinzolamide 3 times a day to the LE and intravenous methylprednisolone (IVMP) 1 g daily for 3 days and pentoxifylline 100 mg twice daily. BCVA at discharge was 5/5 in the RE and 5/8 in the LE. The patient was referred to the cardiology, vascular, and pulmonology clinics for further testing. Two weeks later, the patient presented to the ophthalmology outpatient clinic for post-hospitalization follow-up. BCVA in the LE was only light perception. VEP showed no response, indicating atrophy of the left optic nerve. The patient was referred for another neurological consultation, where no abnormalities were found.

Six months later, the woman returned to the ophthalmology department due to deterioration of vision, this time in the RE. BCVA was 5/10 in the RE and light perception in the LE. Fundoscopic examination of the RE showed a normal optic disc, while the left optic disc was pale. Arterial attenuation was also observed in the LE. Her general physical and systemic examination as well as laboratory tests were normal. Static perimetry in the RE revealed a superior altitudinal VF defect (Figure 1B). FA was unremarkable in both eyes. VEP pattern was normal in the RE, while the LE showed optic disc atrophy (Figure 2C).

Although the patient initially refused to undergo MRI of the brain and orbit with contrast agents, the next day she consented to the examination. Gadolinium-enhanced MRI (Gd-MRI) showed that the right and left optic nerves were the same width.

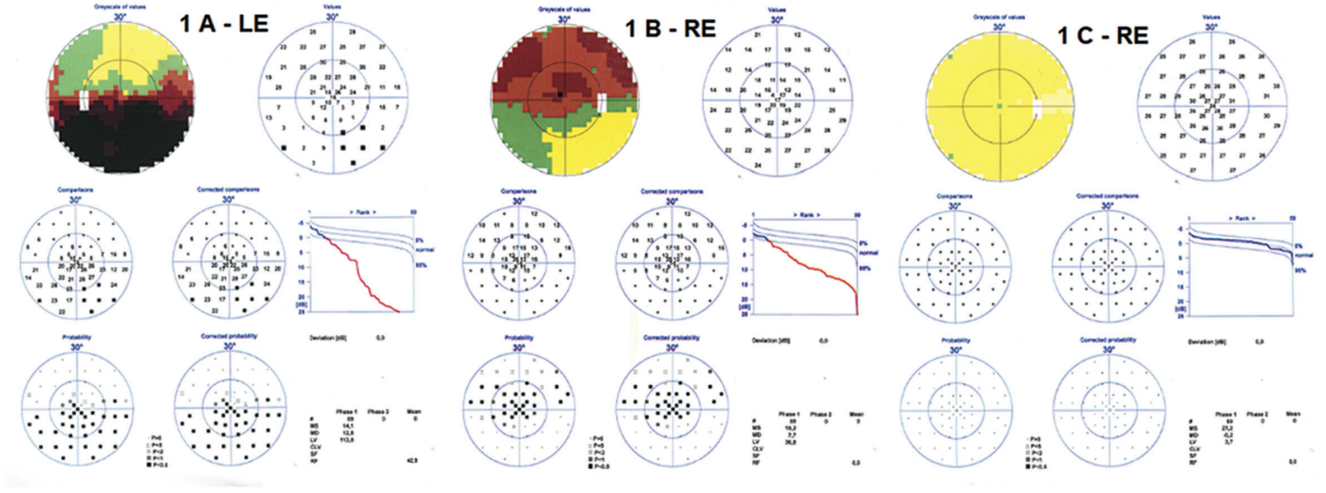

Figure 1. Static perimetry showed inferior altitudinal defect in the left eye (A) and in the right eye revealed superior altitudinal VF defect during the second hospitalization (B) and normal VF two years after discharge (C)
VF: Visual field

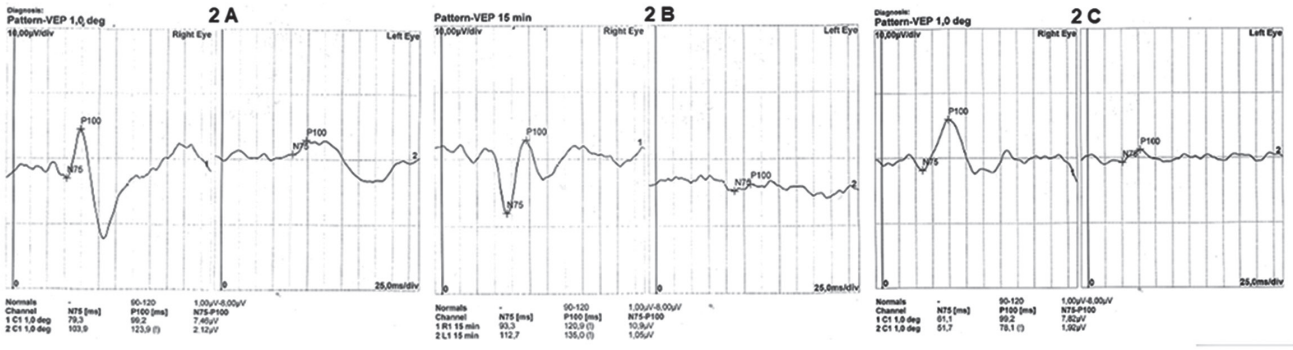

Figure 2. Visual evoked potential was normal for the right eye, while in the left eye, P100 latency was prolonged to 120%, the amplitude after 1° stimulation was 25% (A), response was residual after 15" (B), and the results indicated optic nerve atrophy (C)

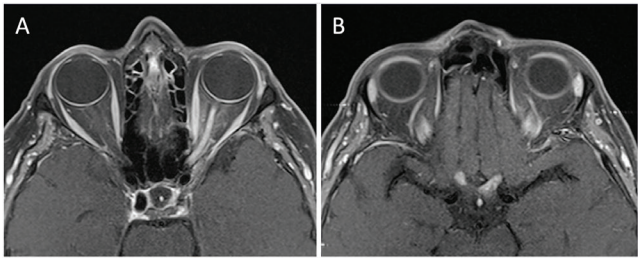

Figure 3. Gadolinium-enhanced magnetic resonance imaging of the brain (A, B) revealed the extended outline of the left part of the optic chiasm and the distal segment of the optic nerve with the cystic lesion. Visible abnormal enhancement after intravenous administration of contrast agent indicating the presence of inflammatory lesions in the left optic nerve, optic chiasm, and the right optic nerve near the optic chiasm

However, the left optic nerve was moderately enhanced after contrast in intraorbital, extraorbital, and optic chiasm sections, indicating active inflammation. The image of the right optic nerve also showed contrast enhancement but only near the optic chiasm (Figure 3A, B).

As the patient had two episodes of acute vision loss within a year, AQP4-IgG antibody testing was done by indirect immunofluorescence and was positive at 1:100 sample dilution, while myelin oligodendrocyte glycoprotein (MOG) IgG was negative. NMOSD was diagnosed and the standard steroid therapy was administered, with a 3-day regimen of daily 1 g IVMP followed by oral tapering over a period of 10 weeks. Gd-MRI showed no signs of longitudinally extensive myelitis in the thoracic or lumbar spinal cord. In addition, the patient was started on oral azathioprine to reduce the risk of further relapse. BCVA at discharge was 5/5 in the RE and light perception in the LE. The patient remains under the care of neurology and ophthalmology clinics, with no recurrences for 2 years (Figure 1C).

Discussion

In 2015, the International Panel for NMO Diagnosis outlined the diagnostic criteria for NMOSD, which consisted of 1) at least one core clinical characteristic (ON, acute myelitis, area postrema syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions, symptomatic cerebral syndrome with NMOSD-typical brain lesions); 2) positive AQP4-IgG test; and 3) exclusion of alternative diagnoses.[8] The key characteristic of NMOSD is the presence of AQP4 antibodies that can penetrate the blood-brain barrier. AQP4 is the main water channel protein predominantly expressed in the cell membrane of astrocytic foot processes, and antibodies against it initiate an immune response, which mediates inflammatory cell infiltration and demyelinating lesions.[2]

The most common manifestation of NMOSD at onset is ON (37-54%; bilateral in 20% of cases), followed by LETM (30-47%).[9] ON in NMOSD, although clinically similar to the attacks seen in MS or isolated ON, is characterized by more severe visual loss associated with more profound neuro-axonal damage. The hallmark of NMOSD is a relapsing course, and the time between relapses is shorter as compared to MS. Relapse occurs in up to 90% of patients and in half of all patients occurs within 1 year of the initial attack,[10] as in the present case.

Screening for AQP4-IgG and MOG-IgG may not be necessary for patients presenting with typical ON. However, the presence of atypical features such as severely impaired visual acuity, rapid progression, recurrent episodes, poor visual recovery, bilateral involvement, non-responsiveness to corticosteroids or corticosteroid dependency, prominent disc edema, perineural optic nerve enhancement, and coexisting extra-optic CNS demyelinating lesions should alert the ophthalmologist to consider alternative causes.[11] Moreover, granulomatous inflammatory conditions, vasculitis, infections, intracranial lesions, and various autoimmune conditions can mimic NMOSD and need to be excluded if the presentation is not typical.[12]

ON represents the most common cause of acute optic neuropathy among patients under 50 years of age.[13] This case report illustrates the diverse clinical manifestation of NMOSD-ON, which can make diagnosis challenging at onset in older patients. The typical age range at NMOSD onset is 32 to 41 years. However, it has been encountered among children and older adults as well.[6] Interestingly, in the majority of LO-NMOSD, the initial presentation is concomitant with findings of myelitis rather than ON.[14] Fundus examination

in NMOSD is usually unremarkable. Only 5-33% of subjects exhibit optic disc edema, whereas optic disc edema with splinter hemorrhage and no cup or small optic disc cup in the fellow eye (referred to as a "disc at risk") are characteristic of NAION.[15,16] Our patient presented "disc at risk" in the second eye at initial presentation. However, no splinter hemorrhage was detected in the first affected eye. The ON Treatment Trial identified diffuse VF loss in two-thirds of affected eyes and central field loss in one-third. Altitudinal VF abnormality, which is considered characteristic of NAION, was present in 8% of participants (in the superior as well as inferior half of the VF).[17] Therefore, the presence of altitudinal VF defect should warrant consideration of ON besides the vascular and compressive causes among the differential diagnoses. Furthermore, normal non-contrast MRI scans as well as the results of VEP and FA in correlation with low BP in our patient mimicked NAION as the most likely etiology in her age group. On the other hand, the dramatic deterioration of vision to LP in our patient after stopping steroids during follow-up is highly uncharacteristic for NAION and should alert the clinician to consider other diagnoses. It is worth noting that also in the case of another ON episode in the other eye, VEP and FA records were unremarkable, which indicates their low usefulness in the differential diagnosis of optic disc edema and that Gd-MRI remains the key examination. The findings of longitudinally extensive optic nerve enhancement with a predilection for the posterior optic pathway and the optic chiasm and/or bilateral optic nerve involvement are atypical and should raise suspicion for NMOSD-ON.[18] However, around 40% of patients with NMOSD may also present with a normal orbital MRI.[19] It should be emphasized that awareness of NMOSD-ON in older patients is crucial in the differential diagnosis of ischemic optic neuropathy.

The gold standard treatment for acute attacks of ON includes high-dose corticosteroids, typically IVMP 1 g/day for 3-5 days, followed by oral steroids to avoid early relapse.[20] In patients not responding to IVMP, plasma exchange (4-9 cycles) should be commenced.[21] Although there is no consensus about the duration of preventive treatment, many experts believe that maintenance therapy should be continued for life.[1] The most commonly used are mycophenolate mofetil, azathioprine, rituximab, methotrexate, and tocilizumab. Most patients achieve remission with one of the first two drugs they try. Importantly, treatment modalities for NMOSD and MS are significantly different. MS disease-modifying treatment (e.g., interferon β, fingolimod, and natalizumab) have been associated with nonresponse or exacerbation in NMOSD,[22] highlighting the importance of early and accurate diagnosis.

NMOSD has a poor prognosis, with a median survival of 8 years from time of diagnosis and overall 10-year mortality of 20-25%.[10] Furthermore, Papathanasiou et al.[5] found that older age at the onset of NMOSD is a predictor of poor outcome, and patients with LO-NMOSD were expected to reach higher Expanded Disability Status Scale score during follow-up compared to those with early onset NMOSD (EO-NMOSD). Thongmee et al.[6] indicated that patients with LO-NMOSD-ON had significantly worse nadir VA at ON onset as well as worse final VA compared to patients with EO-NMOSD-ON. There is no evidence that there is an arbitrary cut-off age at onset, rather clinical phenotypes and disability gradually change with time.[5] Poorer recovery from the attack may be caused by the negative relationship between retinal nerve fiber layer thickness and age, as well as reduced repair mechanisms, impaired immune tolerance, and comorbidities.[7,23]

Early diagnosis and prompt treatment preserve better visual outcomes and prevent the accumulation of severe neurologic disability in patients with NMOSD. Therefore, it is strongly recommended to include LO-NMOSD-ON in the differential diagnosis of acute to subacute optic neuropathy in addition to ischemic optic neuropathy among the middle-aged and older populations.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: D.W-P., L.S., Concept: L.S., M.Ś., D.W-P., Design: M.Ś., L.S., Data Collection or Processing: M.Ś, L.S, Analysis or Interpretation: L.S., M.Ś, D. W-P., Literature Search: M.Ś., L.S., Writing: M.Ś., L.S.

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Case Report

A Rare Case Report of Eight Syndrome Secondary to Syringomyelia Associated with Type I Chiari Malformation

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Abstract

Eight syndrome is defined as the combination of a unilateral conjugate gaze palsy and ipsilateral seventh cranial nerve palsy. It may occur as a result of demyelinating, vascular, infectious, or compressive lesions of the brainstem localized to the caudal pontine tegmentum. A 43-year-old woman was admitted to our clinic with complaints of headache, inability to look to the left, and weakness on the left side of her face. The complaints had begun abruptly about a month before her admission. Suboccipital decompression surgery for type I Chiari malformation had been performed 10 years earlier. Neuro-ophthalmological examination revealed left-sided horizontal gaze palsy and anisocoria. Cranial and cervical magnetic resonance images revealed cerebellar tonsillar herniation and syringomyelia, the latter of which was considered to be the cause of eight syndrome. No interventions were performed, and periodic follow-up was advised on neurosurgical consultation. Left gaze palsy and facial palsy recovered almost completely in three months, while the anisocoria persisted. Syringomyelia should be considered among the causes of horizontal gaze palsy plus ipsilateral seventh nerve palsy, termed as eight syndrome. Clinical suspicion and appropriate radiological examination can aid in the diagnosis.

Keywords: Chiari malformation, eight syndrome, horizontal gaze palsy, seventh cranial nerve palsy

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Introduction

Eight syndrome is described as the combination of a unilateral conjugated gaze palsy and ipsilateral seventh cranial nerve palsy. The syndrome and/or other variants may occur in demyelinating, vascular, infectious, or compressive lesions of the brainstem localized to the caudal pontine tegmentum. The brainstem structures primarily affected are the ipsilateral seventh cranial nerve and paramedian pontine reticular formation/sixth cranial nerve nucleus.[1]

Case Report

A 43-year-old woman presented to our clinic with complaints of headache, inability to look to the left, and weakness on the left side of her face. The complaints had begun abruptly about a month before her admission. Suboccipital decompression surgery for type I Chiari malformation (CM) had been performed 10 years earlier. No other known pre-existing systemic diseases or drug usage was present and her family history was unremarkable. On admission, complete physical examination including vital signs were normal. Neurological examination was unremarkable except for left seventh cranial nerve palsy (Figure 1A). Neuro-ophthalmological examination revealed left-sided horizontal gaze palsy (Figure 1B) and anisocoria. Other extraocular eye movements were within normal limits. Anisocoria was prominent in dim light (pupil diameter: 4 mm right, 3 mm left). However, ptosis was not noted. Pupillary light and near reflexes were normal. Pupillary dilation was not observed on the left side in dim light after instilling topical 0.5% apraclonidine (Iopidine, Alcon, Fort Worth, TX, USA). Cranial magnetic resonance imaging (MRI) performed to assess for a caudal pontine tegmental lesion revealed cerebellar tonsillar herniation and

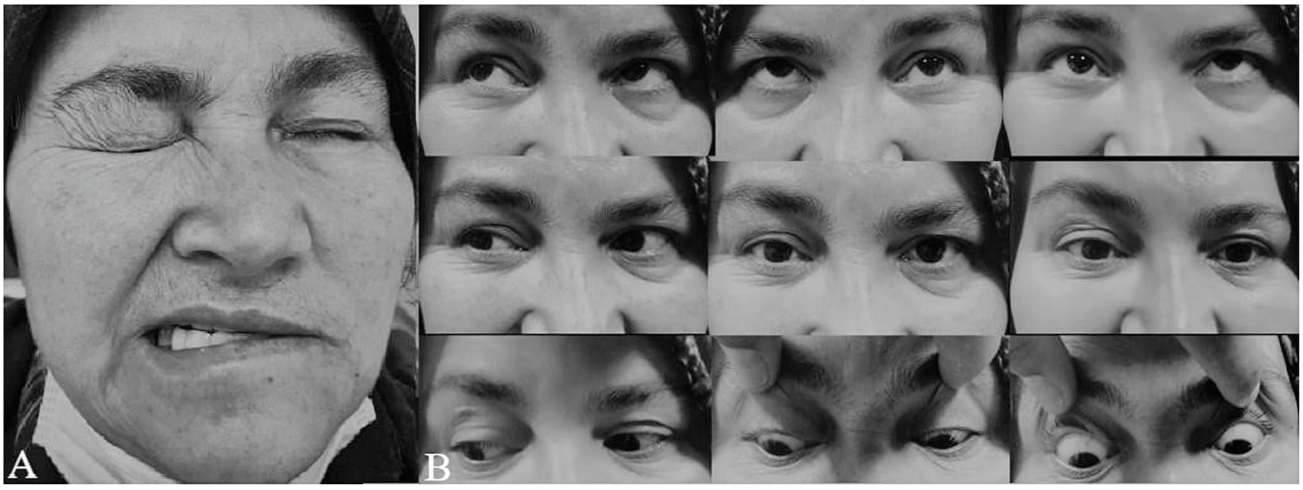

Figure 1. Image showing left peripheral seventh nerve palsy (A) and images of the patient in nine diagnostic gaze positions demonstrating left-sided horizontal gaze palsy (B)

syringomyelia descending from the caudal tegmental region of the pons to the second cervical vertebral level, which was better delineated on cervical MRI (Figure 2). This was considered to be the cause of eight syndrome. Intervention was not considered and periodic follow-up was advised on neurosurgical consultation. Left gaze palsy and facial palsy recovered almost completely in three months, while the anisocoria persisted.

Discussion

Type 1 CM is defined as herniation of the cerebellar tonsils into the upper cervical canal at the level of the foramen magnum. Syringomyelia, a rare neurological condition, often accompanies this craniocervical junction abnormality and is characterized by the presence of a fluid-filled cavity in the central canal of the spinal cord or within its parenchyma.[2,3,4] The prevalence of syringomyelia ranges from 8.4/100,000 to 0.9/10,000 and is commonly observed in patients aged 20 to 50 years.[3]

Apart from type I CM, it can develop as a post-inflammatory or post-traumatic condition, and spinal cord tumors and secondary myelomalacia are among the other known causes.[3,4] Although various theories have been put forward to explain the pathophysiological process, the most valid explanation is impairment of cerebrospinal fluid (CSF) circulation caused by obstruction of the subarachnoid space.[4]

Patients with syringomyelia may present with a wide variety of non-specific symptoms and/or findings depending on the size, location, and extent of the cyst within the spinal cord and/or brainstem. However, some cases are completely asymptomatic and incidentally discovered on radiologic evaluation.[1,2,3,4,5]

Diagnosis is made with clinical suspicion based on symptoms and/or signs. MRI is currently the most widely preferred imaging modality for diagnosis and follow-up. The fluid-filled cavities appear hyperintense on T2-weighted images but remain hypointense on T1-weighted images. In addition to its use in diagnosis and follow-up, MRI also reveals secondary causes such as tumors and type 1 CM that may be associated with syringomyelia.[5]

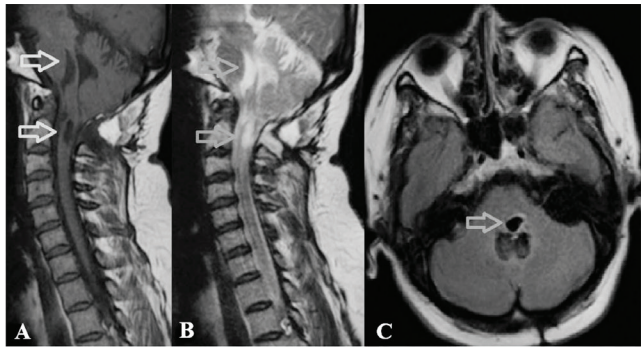

Figure 2. Magnetic resonance imaging (MRI) of the brainstem and spinal cord. T1-weighted (A) and T2-weighted (B) sagittal MRI of the brainstem and spinal cord revealing tonsillar herniation and hypointense (arrows) and hyperintense (arrows) cystic cavity corresponding to syringomyelia, respectively. T1-weighted axial MRI of the brainstem (C) showing the hypointense (arrow) cystic cavity corresponding to syringomyelia in the caudal tegmental region of the pons

Surgical treatment of type 1 CM-related syringomyelia aims to restore normal CSF circulation at the level of foremen magnum, reduce the syrinx, and eliminate the compression exerted by the cerebellar tonsil on the brainstem.[2,3,4,5]

To the best of our knowledge, here we describe the first patient with eight syndrome due to syringomyelia involving the brainstem in the literature. Interestingly, although the patient did not undergo any medical or surgical intervention and the cyst did not change in size, her clinical findings improved during follow-up. We cannot fully explain the abrupt onset and spontaneous clinical improvement in this case. The most plausible explanation may be the fluctuations in cyst volume with alterations in the CSF circulation caused by tonsil herniation.

Syringomyelia should be kept in mind among the causes of horizontal gaze palsy plus ipsilateral seventh nerve palsy, termed as eight syndrome. Clinical suspicion and appropriate radiological examination can aid in the diagnosis.

Ethics

Informed Consent: Informed consent was obtained from the patient for the publication of this report.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: D.T.K., Concept: D.T.K., Ö.K., N.Ç., Design: D.T.K., Ö.K., N.Ç., Data Collection or Processing: D.T.K., Analysis or Interpretation: D.T.K., P.K., Literature Search: P.K., Writing: D.T.K., P.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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