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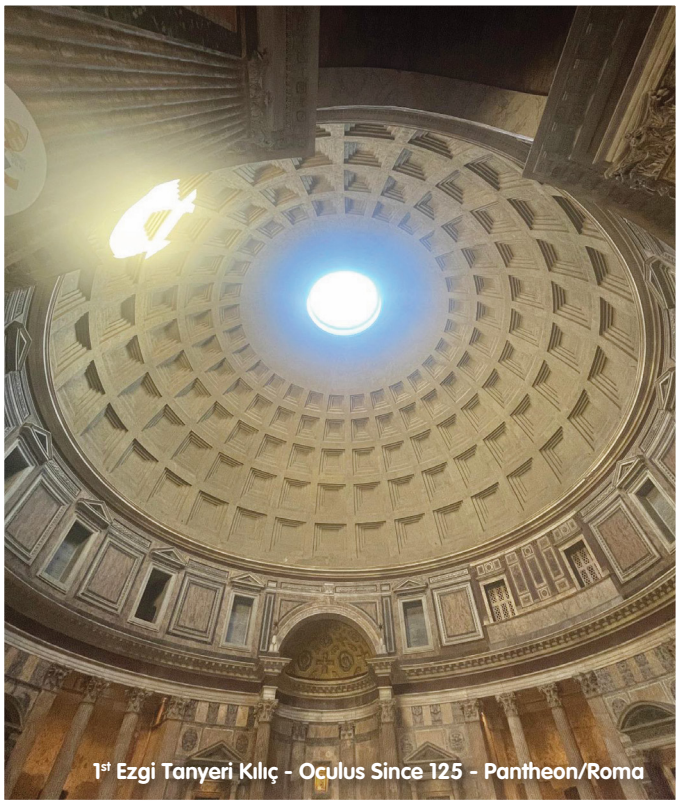

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AT A GLANCE

2025 Issue 1 at a Glance:

Esteemed colleagues,

This issue of our journal features five original research articles, two reviews, and three case reports that we hope you will read with interest and benefit from.

Myopia is a common refractive error worldwide, and the increase in its incidence is regarded as a global epidemic. In addition to the direct economic and social burden of myopia, ocular complications associated with myopia can lead to severe vision loss. In a retrospective study aiming to investigate whether combination therapy with 0.05% atropine and Myopi-X® peripheral progressive addition lenses (PAL; Novax®) provided an additional effect compared to Myopi-X PAL or 0.05% atropine monotherapy, Akagün and Altıparmak compared a total of 51 patients who received Myopi-X PAL (n=27), 0.05% atropine (n=13), or combination 0.05% atropine and Myopi-X PAL (n=11) in terms of baseline characteristics such as age, cycloplegic spherical equivalent (SE), and axial length (AL), as well as SE and AL at 12 months after the start of treatment. They determined that the combination of 0.05% atropine and Myopi-X PAL did not show any additional benefit over the treatments alone (See pages 1-5).

Refractive accommodative esotropia (RAET) is a clinical entity characterized by convergent strabismus due to hypermetropic accommodative convergence. The mainstay of treatment in patients with RAET is full correction of hyperopia with glasses. In their retrospective study, Pelit and Sefi Yurdakul investigated the clinical features and risk factors of children diagnosed with RAET who developed spontaneous consecutive exotropia. They compared the medical records of 19 patients who spontaneously transitioned from RAET to exotropia (XT) and a control group 31 age-matched patients with RAET and spectacle correction of optical alignment for both near and distance. They found that patients with high hyperopia refraction values and those with concomitant inferior oblique overaction were at higher risk of developing XT, and emphasized that patients with these characteristics should remain under long-term follow-up (See pages 6-10).

Abnormal head position (AHP) is an adaptation mechanism in which the head is turned or tilted and the chin may be up or down in order to increase visual acuity, prevent diplopia, or provide comfortable binocular vision. AHP is not a diagnosis but a symptom of an underlying disease, although it may have no apparent cause in some cases. The most common causes of AHP are excessive contraction in the sternocleidomastoid muscle due to congenital muscular torticollis, ocular diseases, and central nervous system anomalies. The main ocular causes are fourth cranial nerve palsy, Duane retraction syndrome, sixth cranial nerve palsy, Brown syndrome, and nystagmus blockage syndrome. In their retrospective study examining the clinical features of patients with ocular AHP and investigating the effect of treatment on the change in AHP in a total of 172 patients (50% females, 50% males) with a mean age of 14.1±13.9 years, Erduran and Niyaz Şahin reported fourth cranial nerve palsy (50%), Duane retraction syndrome (16.9%), and A-V pattern strabismus (15.1%). They pointed out that ophthalmological and orthoptic examinations should be performed in patients with AHP, and strabismus surgery or botulinum toxin administration in eligible patients may reduce or completely correct AHP (See pages 11-15).

Candan et al. conducted a hospital-based epidemiological study aiming to determine the prevalence of the most common retinal vascular diseases and their most common complications in a tertiary hospital for the first time in Türkiye, and thus contribute to the protection of public health and the correct planning of health services and resources. The authors determined the prevalence of retinal vascular diseases as 1.4% in the general population, while the prevalences of diabetic retinopathy, retinal vein occlusion, and retinal artery occlusion, which are the most common retinal vascular diseases, were 1.12%, 0.27%, and 0.01%, respectively (See pages 16-23).

Genç Bozhöyük et al. examined the records of a total of 77 pediatric patients, 58 (75.3%) operated for congenital cataract and 19 (24.7%) for acquired cataract, with at least 1 year of follow-up. They evaluated preoperative strabismus types, changes in strabismus after surgery, and the characteristics of postoperative new-onset strabismus. The authors emphasized that strabismus is common in pediatric cataract, and despite successful surgical treatment, the prevalence of postoperative strabismus onset is high, especially in unilateral cases operated at 1 year of age or younger, which increases the risk of strabismus-related suppression and amblyopia, as well as cataract-related deprivation amblyopia (See pages 24-28).

Climate change is considered one of the biggest threats to global health in the 21st century, and the health sector is known to contribute significantly to the production of greenhouse gases. Ophthalmology, which has the highest number of surgeries in the health system and differs from other branches with its rapid patient circulation, may be responsible for a significant part of this carbon emission burden. In the first review in this issue, Kıyat and Palamar aimed to provide an overview of surgical strategies that can be applied in keratoplasty surgeries to maximize benefit and increase sustainability through efficient resource usage. In corneal transplantation surgeries, the authors state that reducing operating room time, appropriately training ophthalmologists and surgery team, reusing instruments such as trephines and punches, striving to ensure the economic use of surgical materials, and choosing the

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AT A GLANCE

appropriate surgical technique are possible ways to improve sustainability and reduce costs during surgery. However, they point out that while taking measures to reduce costs, the utmost care must be taken to maintain safety and effectiveness in order to achieve a balance between sustainability and patient safety (See pages 29-35).

Pachychoroid diseases are a group of diseases characterized by increased choroidal thickness that share common underlying pathological mechanisms. Eyes presenting with pachychoroidal changes often show dilation in the large choroidal vessels, which causes compression of the overlying choriocapillaris and Sattler's layer. Pathological findings such as pigment epitheliopathy, choroidal neovascularization, submacular serous detachment, significant choroidal and scleral changes can be seen in pachychoroid spectrum diseases. In their review, Demirel et al. provide readers with up-to-date information on imaging methods used in diseases in the pachychoroid spectrum (See pages 36-48).

Korkmaz et al. present a patient with bilateral keratoconus who had a history of intrastromal corneal ring segment placement in the right eye and penetrating keratoplasty (PK) in the left eye and was using hybrid contact lenses. When his bilateral *Acanthamoeba* keratitis could not be diagnosed by microbiological examinations and *in vivo* confocal microscopy (IVCM), he developed corneal perforation on the right and simultaneous wound dehiscence on the left despite medical treatment. Due to the patient's renal failure, he was treated with simultaneous bilateral tectonic therapeutic PK to minimize the risks arising from general anesthesia. The authors pointed out that auxiliary diagnostic tools such as IVCM may be misleading in eyes where the normal anatomy has been altered by surgery, and inconsistency between the results of the diagnostic methods and the patient's clinical picture may delay the diagnosis and necessitate PK (See pages 49-52).

Jeune syndrome (JS), first described as asphyxiating thoracic dystrophy, is an autosomal recessive osteochondrodysplasia with characteristic skeletal abnormalities and variable renal, hepatic, pancreatic, and ocular complications. JS is classified among the hereditary syndromic retinopathies. The main cause of ocular pathologies in JS is genetic mutations in ciliary proteins that prevent normal functioning of the retinal photoreceptor cells. Aksoy and Tigrel describe a case of JS presenting with complaints of poor night vision despite 20/20 visual acuity, pointing out that hereditary retinal dystrophies should be considered in patients with syndromic comorbidities accompanying nyctalopia, even if visual acuity is perfect, and that structural and functional multimodal retinal imaging techniques should be used for diagnosis and genetic counseling should be provided (See pages 53-56).

Knobloch syndrome is a rare genetic disease caused by mutations in the *COL18A1* gene and characterized by extreme myopia, vitreoretinal degeneration, retinal detachment (RD), and occipital encephalocele. Abdullah et al. described a surgical technique using a double layer of human amniotic membrane used in a child with Knobloch syndrome presenting with chronic RD associated with high myopic macular hole and share the advantages and disadvantages of this technique (See pages 57-60).

We hope that the articles in our first issue of this year will make for interesting reading and provide guidance in your professional practice.

Respectfully on behalf of the Editorial Board,
Özlem Yıldırım, MD

Original Article

Combination Therapy with Atropine 0.05% and Myopi-X® Glasses: Is it Effective in Myopia Control?

Nilay Akagün, Uğur Emrah Altıparmak

Acıbadem Ankara Hospital, Clinic of Ophthalmology, Ankara, Türkiye

Abstract

Objectives: To investigate whether the combination therapy of Myopi-X® peripheral progressive addition lenses (PAL; Novax®) and atropine 0.05% provides an additive effect compared to monotherapies with either Myopi-X® PAL or atropine 0.05%.

Materials and Methods: This retrospective cross-sectional study reviewed the clinical records of 51 patients, categorized into three groups: 27 in the Myopi-X group, 13 in the atropine 0.05% group, and 11 in the combination therapy group using Myopi-X peripheral PAL with atropine 0.05%. Baseline characteristics, including age, cycloplegic spherical equivalent (SE), and axial length (AL), were compared between the groups. Twelve months after treatment initiation, changes in SE and AL were assessed and compared between the groups.

Results: Among the 51 patients analyzed, the baseline characteristics differed significantly between the groups, with the atropine 0.05% group showing a higher average age, longer AL, and lower SE compared to the other groups. After 12 months, no significant differences were found in SE changes between the treatment groups (p=0.35). Similarly, changes in AL did not significantly differ between the groups (p=0.10), although age had a significant impact on AL change (p=0.01). No significant differences were observed in pairwise comparisons of SE or AL changes between the groups.

Conclusion: In this study, combining atropine 0.05% with Myopi-X PALs did not provide an additive benefit. The literature suggests that both treatments are effective in slowing myopia progression individually; however, in our study, their combination did not significantly improve SE progression or axial elongation compared to monotherapies. Further randomized studies with larger patient groups are needed to confirm these findings and assess long-term effects.

Keywords: Myopia management, progressive addition lenses (PAL), atropine 0.05% therapy, combination therapies for myopia control

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The study was presented as an oral presentation at the EVER 2024 Valencia meeting. The abstract of our oral presentation has been published in Acta Ophthalmologica, volume 103, issue S284, under the title "Abstracts from the 2024 European Association for Vision and Eye Research Congress, 3-5 November 2024, Valencia- January 2025."

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Introduction

Myopia is a common refractive error worldwide, and its increasing frequency is considered a global epidemic.[1,2] The prevalence of myopia is expected to increase, and it is estimated that by 2050, myopia and high myopia will affect approximately 50% and 10% of the world's population, respectively.[3] In addition to the direct economic and social burden of myopia, the associated ocular complications may lead to substantial visual loss.[4]

Both genetic and environmental factors influence the occurrence and progression of myopia, and some seem to be closely linked. A lack of outdoor activity, high education levels, and prolonged near work are important risk factors.[5] Currently, the main approaches to myopia control include atropine eye drops of varying concentrations, orthokeratology, dual-focus contact lenses, multifocal contact lenses, and myopia control spectacle lenses.[6]

Combination therapy is a common practice in the medical field for optimizing treatment efficacy while minimizing adverse effects. Examples include cancer care, diabetes treatment, and glaucoma management, among many others.[7,8,9,10] Similarly, combining therapies with different mechanisms of action may be more beneficial than monotherapy for reducing the progression of myopia. There are studies in the literature investigating the efficacy of combination treatments aimed at slowing the progression of myopia. Combination therapies involving

orthokeratology and atropine, myopia control spectacle lenses and atropine, as well as multifocal contact lenses and atropine have been trialed, with varying outcomes. In this study, we aimed to investigate whether combining Myopi-X® peripheral progressive addition lenses (PAL; Novax®) with atropine 0.05% therapy provides an additive effect compared to monotherapy with Myopi-X lenses or atropine 0.05%.

Materials and Methods

This retrospective cross-sectional study was approved by the Acıbadem Healthcare Institutions Medical Research Ethics Committee (decision no: 2024-8/302, date: 16.05.2024). Informed consent forms were obtained from the parents/guardians of all patients included in the study. The clinical records of patients who used Myopi-X lenses (group 1), received atropine 0.05% eye drop treatment (group 2), or received combined Myopi-X lenses and atropine 0.05% eye drop treatment (group 3) between November 1, 2022 and November 30, 2023 were reviewed. The inclusion criteria were having an age of 5-16 years at the start of therapy, initial myopic spherical equivalent (SE) between -1 and -9 diopters (D), astigmatism less than 2.0 D, anisometropia less than 1.5 D, and a minimum follow-up of 12 months. Patients with other eye diseases (glaucoma, cataract, keratoconus, and any form of strabismus) or any genetic syndromes were excluded from the study. The records included age, date of visit, prescription, and cycloplegic autorefraction measurements of SE and axial length (AL).

The standard procedure for determining cycloplegic autorefraction was carried out after the instillation of tropicamide 1% (Tropamid® Forte 1% [10 mg/mL], Bilim İlaç). Two drops were instilled into each eye, 5 minutes apart, and refraction was measured 30 minutes later using a Topcon KR-8900 autorefractometer. The device was set to 0.25 D, and the median of the mean from 5 readings per measurement was recorded. AL was measured in each eye using a Zeiss IOLMaster 700 instrument. AL measurements were repeated until the standard deviation (SD) was <0.05.

All atropine eye drops were compounded using the same compounding pharmacy to ensure that the eye drops were at the same concentration. Atropine sulfate (1 mg/1 mL ampoule (Türk Tıpsan®, Ankara, Türkiye) was diluted to a concentration of 0.05% using Eyestil® (sodium hyaluronate 1.5 mg/1 mL; SIFI Pharmaceuticals®, Catania, Italy) in a 10 mL vial.

The primary outcome measures were changes in SE and AL at 12 months.

Statistical Analysis

Continuous variables were summarized as mean with SD. Categorical data were expressed as frequency and percentage. Differences in baseline characteristics across the groups were evaluated by the Kruskal-Wallis test. A generalized linear mixed model (GLMM) was applied to evaluate the treatment effect on SE and AL. The model included treatment and the interaction time by treatment as a fixed effect, age and baseline SE and AL values as fixed covariates, and both eyes and subjects were included as random effects. Two-sided p values less than 0.05 were considered statistically significant. IBM statistics V29.0.1.0 (171) (IBM Corp. Released 2023, Armonk, New York, USA: IBM Corp.) was used for statistical analysis.

Results

The entire dataset comprised 51 patients: 27 in the Myopi-X group, 13 in the atropine 0.05% group, and 11 in the Myopi-X plus atropine 0.05% group. The study sample included 35 (68.6%) girls and 16 (31.4%) boys.

Baseline characteristics are presented in Table 1. Due to the non-random assignment of groups, there were significant differences in some baseline characteristics. Specifically, the atropine 0.05% group was significantly older than both the Myopi-X group and the Myopi-X plus atropine 0.05% group. In terms of baseline SE, the atropine 0.05% group had lower SE values compared to the other two groups. Additionally, the atropine 0.05% group had the highest baseline AL, which was greater than both the Myopi-X group and the Myopi-X plus atropine 0.05% group. Despite these differences, the GLMM analyses were adjusted for baseline age, SE, and AL to account for these variations.

Spherical Equivalent Changes at 12 Months

The treatment groups did not differ significantly in terms of SE change (p=0.35). Age, baseline SE, baseline AL, and treatment group were not significantly associated with SE change (p=0.58, 0.84, 0.13, and 0.17, respectively). Bonferroni-adjusted post-hoc tests for comparisons between the atropine 0.05% group, the Myopi-X group, and the Myopi-X plus atropine 0.05% group did not reveal any significant treatment effects in any of the pairwise comparisons. Specifically, no significant differences in SE were observed between the atropine 0.05% group and the Myopi-X group (p=0.27), between the Myopi-X group and the Myopi-X plus atropine 0.05% group (p=0.93), or between the tropine 0.05% group and the Myopi-X plus atropine 0.05% group (p=0.42) (Table 2, Figure 1).

Table 1. Baseline characteristics of patients in the treatment groups

	Total (n=51)	Atropine 0.05% group (n=13)	Myopi-X group (n=27)	Myopi-X + atropine 0.05% group (n=11)	p value
Age (years)	9.83±2.29	11.31±1.892	9.25±2.14	9.55±2.40	<0.001
Baseline SE (D)	-3.80±2.17	-5.16±2.74	-3.08±1.68	-3.98±1.73	<0.001
Baseline AL (mm)	24.91±1.10	25.69±1.36	24.53±0.78	24.95±0.96	<0.001

Results are presented as mean ± standard deviation. SE: Spherical equivalent, D: Diopters, AL: Axial length

Axial Length Changes at 12 Months

The treatment groups did not differ significantly in terms of AL change (p=0.10). Age had a significant impact on AL change (p=0.01), while baseline SE (p=0.16) and baseline AL (p=0.1) did not show significant effects. Although age significantly affected AL change, different age groups did not exhibit a significant difference in AL change between the three treatment groups over 12 months. Bonferroni-adjusted post-hoc tests for comparisons between the atropine 0.05% group, the Myopi-X group, and the Myopi-X plus atropine 0.05% group did not reveal any significant treatment effects in any of the pairwise comparisons. Specifically, no significant differences were observed in AL change between the atropine 0.05% group and the Myopi-X group (p=0.05), between the Myopi-X group and the Myopi-X plus atropine 0.05% group (p=0.87), or between the atropine 0.05% group and the Myopi-X plus atropine 0.05% group (p=0.21) (Table 2, Figure 2).

Discussion

The results from this 1-year retrospective study indicated that combining atropine 0.05% treatment with Myopi-X peripheral PAL therapy did not show any additive effect on the individual efficacy of these treatments.

PALs slow myopia progression owing to peripheral myopic defocus, which provides an inhibiting signal that slows axial elongation.[11] The design of the Myopi-X lenses is different from that of traditional PALs. The Myopi-X peripheral defocus PALs consist of a central 12-mm optical zone for correcting distance refractive error and a 24-mm transitional circular optical zone with an additive power of 2 or 3 D. It is possible that the peripheral myopic defocus effect of Myopi-X lenses may be higher than that of traditional PALs.

Atropine, a non-specific muscarinic antagonist, has biochemical effects on the sclera that may influence scleral remodeling. Another theory suggests that increased ultraviolet exposure (secondary to pupil dilation) may increase collagen cross-linking within the sclera, thereby limiting scleral growth.[12] A potential mechanism for the combined effect of atropine drops with optical interventions is thought to be the expansion of the peripheral defocus area resulting from pupil dilation, which would enhance the effectiveness of combination therapies compared to monotherapies.[13]

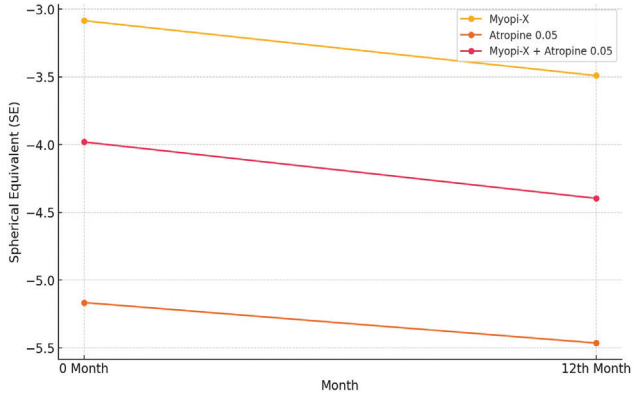

Figure 1. Change in spherical equivalent (in diopters) over 12 months in the different treatment groups

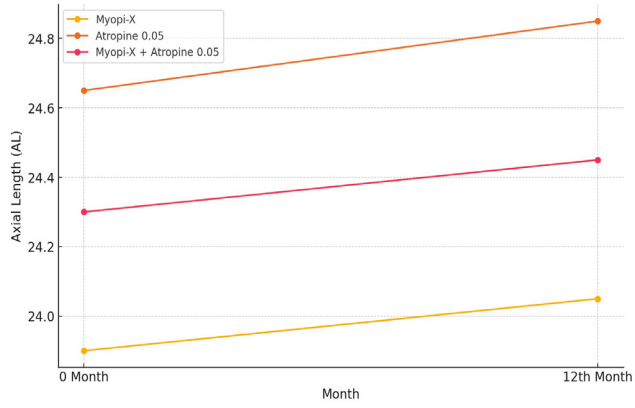

Figure 2. Change in axial length (in mm) over 12 months in the different treatment groups

Table 2. Changes in spherical equivalent and axial length in the Myopi-X, atropine 0.05%, and Myopi-X plus atropine 0.05% groups at 12 months

	Myopi-X® group[1]	Atropine 0.05% group[2]	Myopi-X plus atropine 0.05% group[3]	p values
Change in SE (D)	-0.44±0.07	-0.13±0.11	-0.55±0.22	0.19 1 vs. 2: 0.08 2 vs. 3: 0.16 1 vs. 3: 0.56
Change in AL (mm)	0.23±0.13	0.17±0.19	0.24±0.22	0.10 1 vs. 2: 0.05 2 vs. 3: 0.21 1 vs. 3: 0.87

Results expressed as mean and standard deviation. SE: Spherical equivalent, D: Diopters, AL: Axial length

Erdinest et al.[14] reported that atropine 0.01% alone or a combination of atropine 0.01% with other therapies (PALs and soft contact lenses with peripheral blur) exhibited better efficacy than bifocal spectacles and single vision lenses (SVLs) for SE progression. However, there was no significant difference between atropine monotherapy and atropine combination treatments. Erdinest et al.[15] also conducted a 3-year retrospective study that compared the efficacy of atropine 0.01%, SVL treatment, and dual-focus contact lens with atropine 0.01% combination treatment. The results indicated that there was no significant benefit of combination treatment compared to atropine treatment alone. An important limitation of these studies was the lack of AL measurements. However, AL is the most significant contributor to refractive error and myopia-related visual impairment.[16]

Nucci et al.[17] completed a 1-year unmasked study that compared patients treated with defocus-incorporated multiple segment (DIMS) spectacles, atropine 0.01%, DIMS plus atropine 0.01%, and SVLs. The authors determined that DIMS plus atropine 0.01% demonstrated a significantly better treatment effect than DIMS monotherapy for refractive error but not for AL. Huang et al.[18] conducted a 1-year retrospective study comparing treatment effects among patients treated with DIMS plus atropine 0.01%, DIMS alone, and SVLs. The authors found a greater treatment effect for SE and axial elongation in the combination group. The variations observed between the studies may be linked to the inclusion of Asian patients by Huang et al.[18] and European patients by Nucci et al.[17]

The Bifocal and Atropine in Myopia study indicated that there was no significant additive effect of combining atropine 0.01% with a center distance soft multifocal contact lens (SMCL) with +2.50 add. For SE progression and axial elongation over a 3-year treatment period, the difference between the SMCL and SMCL with atropine groups was not statistically significant.[19]

Kinoshita et al.[20] and Tan et al.[21] investigated the combination of atropine 0.01% plus orthokeratology. Their results showed that axial elongation was significantly slower among participants randomly assigned to the combination treatment than among those who were assigned to orthokeratology alone. However, Chen et al.[22] noted that adding atropine to orthokeratology did not slow the 3-year axial elongation compared to orthokeratology alone after the participants had used orthokeratology monotherapy for a year.

In these studies, atropine 0.01% was employed. Most research indicates that combining 0.01% atropine with optical interventions yields added treatment benefits. However, this extra decrease in ocular growth may be limited to the first 6-month treatment period.

The use of atropine, particularly at lower concentrations, has gained interest because of its efficacy in slowing myopia progression, with minimal side effects.[23] According to the findings from the three-phase low-concentration atropine for myopia progression study, 0.05% atropine has emerged as the most effective concentration for controlling myopia progression in children. This concentration was found to significantly slow the progression of myopia and axial elongation over a three-year period.[24,25] Based on these results, it can be hypothesized that changing the treatment from atropine 0.01% to 0.05% in combination therapies may alter the outcomes.

Erdinest et al.[26] reported the efficacy of combined 0.05% atropine and MF60 contact lens therapy for the first time in the literature. The study compared the efficacy of three treatment groups: the atropine 0.05% plus MF60 contact lens group, the MF60 contact lenses monotherapy group, and the SVL control group. Both the atropine 0.05% plus the MF60 contact lens group and the MF60 contact lens monotherapy group demonstrated superior efficacy compared to the control group. However, there was no significant difference between the atropine 0.05% plus MF60 contact lens group and MF60 contact lens groups. From these results, it can be speculated that atropine 0.05% and MF60 contact lens combination treatment did not have an additive effect on MF60 contact lens therapy alone. These outcomes are similar to those of the present study.

Combination therapies in medicine involve the use of two or more treatment modalities to synergistically target a disease or a condition. Combining various treatments with complementary mechanisms of action can enhance therapeutic efficacy. However, in some cases, combining therapies with conflicting mechanisms of action may lead to antagonistic effects, ultimately reducing or failing to alter overall therapeutic efficacy. The lack of an additive effect of combined atropine and PAL therapy over monotherapies may be attributed to an unknown antagonistic effect.

In conclusion, there is limited literature available on combination therapies for slowing myopia progression. Based on PubMed results, this study provides new insights by exploring the use of atropine 0.05%, rather than the more commonly used 0.01%, within a combination treatment protocol. Furthermore, this study contributes to understanding the potential additive effects of combining 0.05% atropine with PALs in slowing axial elongation in children with myopia.

Study Limitations

Our study has several important limitations. First, its retrospective design and small sample sizes within each treatment group may limit the generalizability of the findings. Additionally, baseline differences between the groups could influence the results. In this study, cycloplegic autorefractometer measurements were used to assess refractive status. While cycloplegic retinoscopy and subjective refraction are often considered gold standards, autorefractometry is commonly employed in myopia management research due to its repeatability and practicality, particularly in studies with large samples. We acknowledge that autorefractometry may lack the precision of other methods, so these findings should be interpreted in light of this limitation. Finally, our study does not address questions of long-term efficacy. Further randomized clinical trials with larger sample sizes are essential to reduce bias and provide more robust conclusions.

Conclusion

In this study, the combination of atropine 0.05% with Myopi-X PALs did not show any additive effect compared to the individual efficacy of each treatment. Although the literature suggests that both therapies independently slow myopia progression, their combination did not provide significant benefits in terms of SE progression or axial elongation in our study. These findings are consistent with other studies demonstrating limited additive effects when combining atropine with optical interventions. Further randomized trials are needed to confirm these results and explore potential long-term outcomes in larger patient groups.

Ethics

Ethics Committee Approval: Acıbadem Healthcare Institutions Medical Research Ethics Committee (decision no: 2024-8/302, date: 16.05.2024).

Informed Consent: Obtained.

Declarations

Authorship Contributions

Surgical and Medical Practices: N.A., U.E.A., Concept: N.A., Design: N.A., Data Collection or Processing: N.A., Analysis or Interpretation: N.A., U.E.A., Literature Search: N.A., Writing: N.A.

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

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Original Article

Clinical Characteristics and Analysis of Spontaneous Consecutive Exotropia in Children with Refractive Accommodative Esotropia

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Abstract

Objectives: To assess the clinical characteristics and risk factors associated with spontaneous consecutive exotropia (ScXT) in children diagnosed with refractive accommodative esotropia (RAET).

Materials and Methods: A retrospective analysis of medical records was conducted on 19 patients who demonstrated a spontaneous transition from RAET to exotropia (XT). Patients who received strabismus surgery or botulinum toxin injection were excluded from the study. The control group consisted of 31 age-matched patients with RAET who demonstrated successful optical alignment at both near and distance. The ophthalmological examination findings of the study and control groups were compared. Independent two-sample t-test and Pearson's chi-square test were used to evaluate the data of the patients.

Results: The study examined patients diagnosed with RAET who developed consecutive XT. Among them, 15 (78.9%) were female and 4 (21.1%) were male. The mean age at esotropia (ET) onset was 22.68 months (standard deviation [SD]: 12.91). The control group consisted of 16 (51.6%) female and 15 (48.4%) male patients, with a mean age at ET onset of 25.09 months (SD: 15.47). Mean age at onset did not differ between the groups (p=0.55). The mean interval between ET onset and appearance of XT was 7.53 years (SD: 1.49). Cycloplegic refraction measurements taken during the initial examination indicated that the study group exhibited greater degrees of hypermetropia in their right (p=0.01) and left (p=0.04) eyes than did the control group. Furthermore, the incidence of inferior oblique muscle overaction was higher among the study group (p=0.03).

Conclusion: The findings indicate that patients with high hypermetropic refraction values should be monitored for an extended period due to the increased risk of developing subsequent XT. Concomitant inferior oblique overaction can increase the risk of ScXT.

Keywords: Spontaneous consecutive exotropia, hypermetropia, refractive accommodative esotropia, inferior oblique overaction

Introduction

Refractive accommodative esotropia (RAET) is a condition characterized by convergent strabismus that occurs due to accommodative convergence (AC) to hypermetropia. It is important to note that the AC/accommodation (A) ratio is normal. The mainstay of treatment in patients with RAET is the full correction of hyperopia with spectacles. Treatment should also be initiated if patients have amblyopia.[1,2,3]

The development of spontaneous consecutive exotropia (ScXT) differs from consecutive exotropia (XT) that occurs after strabismus surgery for esotropia (ET). The onset is gradual, and diplopia is not typically present. ScXT has been observed in 5% to 15% of patients with RAET following weeks to a mean of 5.5 years of full hyperopic correction.[1,4,5] High hyperopia of +5 diopter (D) or more, early onset of ET, initial amblyopia, weak or absent binocular single vision, a decrease in the AC/A ratio, and fusional vergence dysfunction have been suggested as triggers of ScXT.[6,7,8,9,10] A review of the literature reveals no reports on the association between inferior oblique muscle overaction (IOOA) and consecutive XT.

The purpose of this retrospective study was to analyze the clinical features of patients with RAET who developed ScXT.

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Materials and Methods

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Başkent University (project no: KA21/538, date: 04.01.2022). As it was a retrospective study, there was no need to obtain informed consent from the subjects. The records of patients with RAET corrected with spectacles were retrospectively reviewed, and those who developed ScXT were included in the study group. Patients with previous ocular surgery, botulinum toxin injection, and history of any systemic (neurological impairment or developmental delay) and ocular disease were excluded from the study. Age-matched patients with RAET who had maintained successful near and distance ocular alignment were included as the control group.

All patients underwent visual acuity testing, assessment of duction and versions, cycloplegic refraction, and anterior and posterior segment examination during follow-up.

Cycloplegic refraction was performed after two instillations of 1% cyclopentolate (Sikloplejin, Alcon Laboratories, Inc., Fort Worth, TX, USA) and 1% tropicamide (Tropamid, Bilim Pharmaceuticals, İstanbul, Türkiye) combination eye drops at 5-minute intervals. After maximum cycloplegia, manifest refraction was performed by retinoscopy and full hypermetropic correction was prescribed. The spherical equivalent (SE) refractive error was calculated as the sum of the SE plus half of the cylindrical power.

Anisometropia was defined as a difference of 1.5 D or more in SE refractive error between the eyes. Amblyopia was diagnosed when visual acuity was reduced by two lines or more in Snellen acuity or when central, steady, and maintained fixation was absent. Amblyopia was treated with occlusion therapy.

Ocular alignment was assessed by the cover and uncover test. The alternate prism cover test or Krimsky test was used to measure the angle of deviation in the primary position at near and distance fixation. Fusion was tested with the Worth four-dot test, and the Titmus fly stereo test (Stereo Optical Co., Inc., Chicago, IL, USA) was used to assess stereoacuity when cooperation was adequate.

Statistical Analysis

Patient data are expressed as number and percentage or as mean, standard deviation (SD), and range. Comparisons between the groups were made using independent two-sample t-test and Pearson's chi-square test. SPSS Statistics version 21 (IBM Corp., Armonk, NY, USA) was used. A p value less than 0.05 was considered statistically significant.

Results

Of the 19 patients with RAET who developed ScXT evaluated in this study, 15 (78.9%) were female and 4 (21.1%) were male. The control group consisted of 31 RAET patients without ScXT, 16 (51.6%) of whom were female and 15 (48.4%) were male. The demographic information and clinical characteristics of the groups are shown in Tables 1 and 2, respectively.

The mean age at onset of ET was 22.68 months (SD: 12.91, range 6-48 months) in the study group and 25.09 months (SD: 15.47, range 6-60 months) in the control group (p=0.55). The mean age at first eye examination in these groups was 31.89 months (SD: 14.42, range 12-60 months) and 34.25 months (SD: 14.79, range 12-72 months), respectively (p=0.45).

In the study group, the mean age at ScXT diagnosis was 9.42 years (SD: 3.41, range 4-13 years). The mean interval between ET onset and appearance of XT was 7.53 years (SD: 1.49 years).

The mean initial cycloplegic SE refractive error values in the study group were +5.72 D (SD: 1.85, range 3.25-8.00 D) for the right eye and +5.50 D (SD: 1.70, range 3.25-9.00 D) for the left eye. In the control group, these values were +4.41 D (SD: 1.78, range 2.75-8.75) for the right eye and +4.50 D (SD: 1.89, range 2.00-9.00) for the left eye. Initial cycloplegic refraction values showed that the study group had higher hyperopic values in the right (p=0.01) and left (p=0.04) eyes compared to the control group.

IOOA was present in 4 patients in the study group and 2 patients in the control group (p=0.03).

At initial presentation, 12 of 19 patients in the study group and 24 of 31 patients in the control group had amblyopia (p=0.36). All patients were treated with occlusion therapy. Anisometropia was detected at baseline in 6 patients in the ScXT group and 12 patients in the control group (p=0.61).

For near vision, the mean angle of esodeviation without spectacle correction was 32.69 prism diopters (PD) (SD: 9.50, range 16-40 PD) in the study group and 33.90 PD (SD: 13.65, range 16-80 PD) in the control group (p=0.34). With spectacle correction, the mean angle of esodeviation for near was 7.42 PD (SD: 0.97, range 4-8 PD) in the study group and 7.09 PD (SD: 1.77, range 0-8 PD) in the control group (p=0.24).

For distance, the mean angle of esodeviation without spectacle correction was 26.11 PD (SD: 7.80, range 14-40 PD) in the study group and 29.48 PD (SD: 13.92, range 10-75 PD) in the control group (p=0.96). With spectacle correction, the mean angle of esodeviation for distance was 4.57 PD (SD: 2.50, range 0-8 PD) in the study group and 4.83 PD (SD: 1.98, range 0-8 PD) in the control group (p=0.65).

We were able to perform the fusion and fly test on initial examination in 13 children in the study group and in 19 children in the control group. When comparing the initial fusion and the fly test, no difference was observed (p=0.44 and p=0.51, respectively).

ScXT was treated with reduced hypermetropia in 18 patients to stimulate AC. Despite undercorrection, one patient deteriorated to large angle XT and underwent surgery.

Mean follow-up was 74.10 months (SD: 46.74, range 23-204 months) in the ScXT group and 70.67 months (SD: 41.05, range 15-142 months) in the control group (p=0.93).

Table 1. Demographic data of the study and control groups			
	Study group (n=19)	**Control group (n=31)**	**p**
Sex			
Female	15 (78.9)	16 (51.6)	
Male	4 (21.1)	15 (48.4)	
Family history			
Strabismus	2 (10.5)	6 (19.4)	0.51
Amblyopia	2 (10.5)	6 (19.4)	0.51
Age at esotropia onset (months)	22.68±12.91 (6-48)	25.09±15.47 (6-60)	0.55
Age at initial visit (months)	31.89±14.42 (12-60)	34.25±14.79 (12-72)	0.45
Follow-up period (months)	74.10±46.74 (23-204)	70.67±41.05 (15-142)	0.93
Data are presented as number and percentage (Pearson's chi-square test) or mean ± standard deviation (range) (independent two-sample t-test)			

Table 2. Clinical features of the study and control groups			
	Study group (n=19)	**Control group (n=31)**	**p**
Cycloplegic refraction at initial visit (SE, D)			
Right eye	5.72±1.85 (3.25-8.00)	4.41±1.78 (2.75-8.75)	**0.01**
Left eye	5.50±1.70 (3.25-9.00)	4.50±1.89 (2.00-9.00)	**0.04**
Cycloplegic refraction at last visit (SE, D)			
Right eye	4.93±1.78 (1.50-7.50)	4.89±1.81 (2.25-10.00)	0.94
Left eye	4.88±1.81 (1.00-7.00)	4.92±2.10 (2.25-10.50)	0.93
Anisometropia	6 (31.6)	12 (38.7)	0.61
Amblyopia	12 (63.2)	24 (77.4)	0.36
Ocular patch treatment	12 (63.2)	24 (77.4)	0.36
Stereopsis*	2/13 (15.4)	6/19 (31.6)	0.51
Worth four-dot test fusion*	2/13 (15.4)	7/19 (36.8)	**0.44**
Inferior oblique overaction	4 (21.1)	2 (6.5)	**0.03**
Dissociated vertical deviation	0 (0)	0 (0)	
Angle of esodeviation at initial visit (without spectacles), (PD)			
Distance	26.11±7.80 (14-40)	29.48±13.92 (10-75)	0.96
Near	32.69±9.50 (16-40)	33.90±13.65 (16-80)	0.34
Angle of esodeviation at initial visit (with glasses), (PD)			
Distance	4.57±2.50 (0-8)	4.83±1.98 (0-8)	0.65
Near	7.42±0.97 (4-8)	7.09±1.77 (0-8)	0.24
Data are presented as number and percentage (Pearson's chi-square test) or mean ± standard deviation (range) (independent two-sample t-test). *Percentages given for the subsets of patients that could be tested, SE: Spherical equivalent, D: Diopter, PD: Prism diopter			

Discussion

ScXT is not uncommon in patients with RAET after correction of hyperopia without botulinum toxin injection or strabismus surgery.[9] Possible risk factors that may trigger the development of ScXT are high hypermetropic refraction, anisometropia, amblyopia, early onset of ET, vertical incomitance, lack of binocular single vision, decreased AC/A ratio, and fusional vergence abnormalities.[6,7,8,9]

Many previous studies have reported that high hyperopia of +5 D or more is considered to be the main cause of ScXT in RAET patients.[6,8-11] In the present study, highly hypermetropic refraction was found to be significantly more prevalent in the ScXT group than in the control group at the initial visit. Our patients in the study group had more than +5 D of hyperopia in each eye.

Senior et al.[9] determined that ET onset occurred before the age of 2 years in patients with ScXT. Contrary to their results, Watanabe-Numata et al.[4] reported that the age of correction was not a risk factor for ScXT. The age at onset of ET in the ScXT group in this study was similar to that in the study by Senior et al.[9] In our study, the age at onset in the study group was 22.7 months. There was no difference in onset age when compared to the control group. However, onset before the age of 2 years with more than +5 D of hyperopia might increase the chance of conversion to ScXT. In addition, early-onset ET without the protection of binocular single vision may contribute to conversion to ScXT.

Watanabe-Numata et al.[4] reported that the prevalence of amblyopia at the first visit was 89% in the ScXT group. Swan[5] reported that all RAET patients with monocular amblyopia progressed to ScXT. However, some studies found that amblyopia was not an important factor in the development of ScXT.[6,10,12] Similarly, we found that there was no statistical difference between the ScXT and control groups in terms of amblyopia.

Ciner and Herzberg[13] reported that ScXT can develop in childhood or much later in adulthood as the amplitude of A decreases. In the current study, the mean age at onset of ScXT was 9.42 years. This is consistent with the study by Moore[12], who reported a mean age at onset of 9 years.

It is difficult to estimate the exact time of onset of consecutive XT, as this information was not well recalled by patients or their relatives, so subjective descriptions of the timing of ScXT should be treated with some skepticism.[14] Beneish et al.[6] reported that the mean interval between the first ET and the appearance of ScXT was 20 months. Berk et al.[1] reported that ScXT developed an average of 5.5 years after hyperopic correction. Mohan and Sharma[15] found that patients with RAET treated with hyperopic correction alone developed ScXT at a mean follow-up of 6.70 years. In the current study, the mean time from initial diagnosis to development of ScXT was 7.53 years. The mean development time of consecutive XT was found to exceed the times reported in the literature. Therefore, long-term follow-up is necessary even if RAET is well corrected with hyperopic spectacles.

Some studies have evaluated vertical incomitance such as dissociated vertical deviation (DVD) and IOOA as risk factors for consecutive XT after ET surgery.[10,16] Patients with vertical incomitance are reported to have a higher chance of fusional vergence abnormalities leading to consecutive XT. The results of our study indicate that the prevalence of IOOA was significantly higher in patients with ScXT compared to the control group. This study is the first to document an association between IOOA and consecutive XT. Shin et al.[10] found that the presence of DVD was higher in their ScXT patients than in the control group. We did not detect DVD in either the study or control groups in our study, which we attribute to the relatively small number of cases.

Weir et al.[17] reported that the development of ScXT is not precluded by the presence of some level of binocular vision. Shin et al.[10] found no statistically significant results when comparing sensory fusion using the Worth four-dot test between the ScXT group and the control group. In the present study, we did not observe any significant between-group differences in sensory fusion using the Worth four-dot test or stereopsis using the stereo fly test.

The management of ScXT in RAET patients can be both conservative or surgical. Six out of 9 patients in the study by Watanabe-Numata et al.[4] underwent strabismus surgery. Berk et al.[1] observed that 62% of ScXT patients exhibited complete resolution upon hyperopia reduction while 12.5% had to resort to surgery. According to the findings of Beneish et al.[6], early recognition and hyperopia reduction by 50-60% could improve ScXT in patients with RAET. In the present study, only one patient (5.3%) underwent strabismus surgery, while in the other 18 patients (94.7%), ScXT improved after reducing hyperopia correction.

Study Limitations

The limitations of the study are that it was not carried out in a large population and that it was a retrospective study.

Conclusion

The present study indicates that high hyperopia and IOOA are risk factors for the development of ScXT. Further prospective studies with larger populations and long-term follow-up periods are necessary to determine if the degree of hyperopia and vertical incomitance are significantly associated with ScXT development.

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Ethics

Ethics Committee Approval: This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Başkent University (project no: KA21/538, date: 04.01.2022).

Informed Consent: Retrospective study.

Declarations

Authorship Contributions

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

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Original Article

Screening of Clinical Data of Patients with Abnormal Head Posture and Investigation of Abnormal Head Posture Change After Treatment

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Abstract

Objectives: To analyze the clinical characteristics of patients with abnormal head posture (AHP) due to ocular causes and investigate the effect of treatment on the change in AHP.

Materials and Methods: Patients with AHP admitted to the strabismus unit of our clinic between 2011 and 2022 were retrospectively analyzed. The patients' clinical and demographic data and change in AHP after treatment were recorded.

Results: A total of 172 patients, 86 females (50%) and 86 males (50%), with a mean age of 14.1±13.9 years were included in the study. The most common ocular causes of AHP were fourth cranial nerve palsy (50%), Duane retraction syndrome (16.9%), and A-V pattern strabismus (15.1%). Sixth cranial nerve palsy, third cranial nerve palsy, nystagmus blockade syndrome, extraocular muscle fibrosis, Brown syndrome, oculocutaneous albinism, and heavy eye syndrome were diagnosed less frequently. The most common AHP type was head tilted position (52.3%), followed by head turned (40.1%), chin down/up (3.5%), and combined form (4.1%). There was a significant relationship between AHP type and diagnosis ($p<0.001$). Amblyopia was present in 55 (35.7%) and absent in 99 (64.3%) patients. There was a significant relationship between amblyopia and both diagnosis ($p<0.001$) and AHP type ($p=0.003$). Of 172 patients, 100 (58.1%) underwent strabismus surgery, 10 (5.8%) had botulinum toxin injection, and 2 (1.2%) were prescribed prism glasses. Sixty patients (34.9%) were only followed up. Among 94 patients who continued follow-up, AHP was reduced in 77.3% and completely resolved in 16.7% of patients treated surgically, and was reduced in 50% and completely resolved in 25% of those treated with botulinum toxin.

Conclusion: The causes of AHP are varied. Ophthalmological and orthoptic examinations should be performed in patients presenting with AHP, and strabismus surgery or botulinum toxin administration may reduce or completely correct AHP in eligible patients.

Keywords: Abnormal head posture, strabismus, strabismus surgery, botulinum toxin, amblyopia

Introduction

Abnormal head posture (AHP) is an adaptation mechanism in which the head may be turned or tilted and the chin up or down in order to increase visual acuity, prevent diplopia, or provide comfortable binocular vision.[1] AHP is not a diagnosis but a symptom of an underlying disease, although there may be no apparent cause in some patients.[2] The main etiologies of AHP are excessive contraction of the sternocleidomastoid muscle due to congenital muscular torticollis, ocular diseases, and central nervous system anomalies.[3] The most common ocular causes are fourth cranial nerve palsy, Duane retraction syndrome, sixth cranial nerve palsy, Brown syndrome, and nystagmus blockage syndrome.[3]

While there are studies examining the types and causes of AHP in the literature, fewer studies have also examined the changes in AHP after treatment. This study aimed to examine the AHP types, etiologies, and clinical data of patients with AHP together with the changes in AHP observed after different treatment options.

Materials and Methods

We retrospectively analyzed the data of 172 patients with AHP who presented to the strabismus unit of the Ondokuz Mayıs University Faculty of Medicine Hospital, Department of Ophthalmology between 2011 and 2022. Our study was

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conducted in accordance with the 2013 Helsinki Declaration and received approval from the Ethics Committee of Ondokuz Mayıs University (decision no: OMÜ KAEK 2022/563, date: 28.12.2022).

Patients who had previously undergone ocular surgery and those whose AHP was due to non-ocular causes were not included in the study. The patients' age, sex, comorbidity, best-corrected visual acuity on Snellen chart, AHP type, eye movements, and amount of deviation measured by prism or Krimsky test were recorded. We also analyzed the results of Worth 4-dot, fusion, and Titmus three-dimensional stereo tests performed before AHP correction.

Based on the patients' diagnosis and examination findings, they were either followed up without treatment or treated with botulinum toxin A (Botox; Allergan Inc., Irvine, CA, USA), prismatic glasses, or surgical methods such as inferior oblique recession, superior oblique tenotomy, inferior oblique tenotomy, and medial/lateral rectus recession or resection.

Statistical Analysis

Descriptive statistics were expressed using mean and standard deviation for continuous variables and as number and percentage for categorical variables. Relationships between categorical variables were examined using chi-square and Cramer's V tests. The study data were analyzed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). P values less than 0.05 were considered statistically significant.

Results

The mean age of the 172 patients with ocular AHP was 14.14±13.95 years (range, 4 months-61 years); 86 (50%) were female and 86 (50%) were male. The distribution of AHPs and clinical data according to diagnosis are summarized in Table 1. The most common diagnoses were fourth cranial nerve palsy (50%), Duane retraction syndrome (16.9%), A-V pattern strabismus (15.1%), sixth cranial nerve palsy (4.1%), and nystagmus blockage syndrome (4.1%). Less common etiologies were third cranial nerve palsy, extraocular muscle fibrosis, Brown syndrome, oculocutaneous albinism, and heavy eye syndrome. In terms of AHP type, there were 90 patients (52.3%) with head tilt, 69 patients (40.1%) with head turn, 6 patients (3.5%) with chin down or up, and 7 patients (4.1%) with combined AHP. There was a significant relationship between the type of AHP patients developed and their diagnosis ($p<0.001$).

Best corrected visual acuity could be measured in 154 of the 172 patients included in the study. Fifty-five (35.7%) of the patients had amblyopia and 99 (64.3%) did not. Among the patients in whom amblyopia could be assessed, amblyopia was observed in all patients diagnosed with nystagmus blockage syndrome, oculocutaneous albinism, heavy eye syndrome, and extraocular muscle fibrosis, whereas amblyopia was not observed in any of the patients with sixth cranial nerve palsy or Brown syndrome. Of the 55 patients with amblyopia, 28 (50.9%) had head turn, 20 (36.4%) had head tilt, 4 (7.3%) had chin down/up, and 3 (5.5%) had combined AHP. The frequency of amblyopia differed significantly according to both diagnosis ($p<0.001$) and AHP type ($p=0.003$).

No deviation in primary position was observed in 53 (30.8%) of the patients, whereas 57 (33.1%) had esotropia, 20 (11.6%) had exotropia, 33 (19.2%) had vertical deviation, and 9 (5.2%) had vertical and horizontal deviation together. Of 108 patients who could undergo the Worth 4-dot test, fusion was observed in 33 (30.6%), suppression in 59 (54.6%), and diplopia in 16 (14.8%). No significant relationship was found between Worth 4-dot test result and amblyopia ($p=0.101$). Stereopsis was observed in 56.4% of 78 patients who could be assessed. Of the 167 patients whose eye movements could be evaluated, 83.2% had some degree of limitation in at least one direction.

Of the 172 patients, 100 (58.1%) underwent strabismus surgery, 10 (5.8%) received botulinum toxin injection, and 2 (1.2%) received prismatic glasses. Sixty patients (34.9%) were followed up without intervention. Of the patients who underwent surgery, 71 (71%) had fourth cranial nerve palsy, 12 (12%) had Duane retraction syndrome, 9 (9%) had A-V pattern strabismus, 4 (4%) had third cranial nerve palsy, 2 (2%) had Brown syndrome, 1 (1%) had extraocular muscle fibrosis, and 1 (1%) had heavy eye syndrome. Of the patients who received botulinum toxin, 4 (40%) had sixth cranial nerve palsy, 4 (40%) had Duane retraction syndrome, 1 (10%) had fourth cranial nerve palsy, and 1 (10%) had extraocular muscle fibrosis.

Final head position could be evaluated in 94 patients who continued regular follow-up. Of these, AHP was reduced in 55 patients (58.5%), completely resolved in 12 patients (12.8%), and remained the same in 27 patients (28.7%). Table 2 shows changes in AHP according to treatment method for the 94 patients who had regular follow-up. AHP improved or decreased in 44 of 71 patients with fourth cranial nerve palsy, 8 of 12 patients with Duane retraction syndrome, 6 of 9 patients with A-V pattern strabismus, 2 of 4 patients with third cranial nerve palsy, and the 1 patient with heavy eye syndrome.

Discussion

AHP refers to a head position that deviates from the normal angle to the body in the vertical, horizontal, and/or anterior-posterior axis.[4] The prevalence of ocular causes of AHP has been reported to be 18-25%.[3] In a study investigating ocular causes of AHP, Erkan Turan et al.[5] determined that paralytic strabismus, nystagmus, and Duane retraction syndrome were the most common. Dikici and Kızılkaya[6] showed in their study that the most common mechanism of AHP was conditions associated with incomitance, with paralytic strabismus being the most common cause (48.6%). Among these conditions, superior oblique palsy and third cranial nerve palsy were the most common causes of vertical incomitance, while sixth cranial nerve palsy and Duane retraction syndrome were the leading causes of horizontal incomitance.[6] Mitchell[7] demonstrated incomitant causes in the etiology of 52.4% of AHP cases. Similar to these studies, we observed that incomitant causes were frequently involved in the etiology of AHP, and fourth cranial nerve palsy and Duane retraction syndrome were the two most common causes in this study.

Table 1. Distribution of AHP types, treatment methods, and clinical findings by diagnosis (n=172)

Diagnosis	Frequency, % (n)	AHP type, % (n)	Amblyopia, % (n)	Treatment method, % (n)	Deviation in primary position (%)	Binocularity, % (n)
Fourth nerve palsy	50 (86)	Head turned: 7 (6) Head tilted: 90.7 (78) Chin down/up: 1.2 (1) Combined: 1.2 (1)	26.2 (21/80)	Surgery: 82.6 (71) BT: 1.2 (1) Follow-up: 16.3 (14)	Orthotropia (43) Vertical deviation (32.6) Esotropia (16.3) Esotropia + vertical deviation (3.5) Exotropia + vertical deviation (2.3) Exotropia (2.3)	Fusion: 31 (18/58) Stereopsis: 70.8 (34/48)
Duane retraction syndrome	16.9 (29)	Head turned: 93.1 (27) Combined: 6.9 (2)	26.9 (7/26)	Follow-up: 44.8 (13) Surgery: 41.4 (12) BT: 13.8 (4)	Esotropia (55.2) Orthotropia (31) Exotropia (6.9) Vertical deviation (3.4) Esotropia + vertical deviation (3.4)	Fusion: 41.1 (7/17) Stereopsis: 100 (12/12)
A-V pattern strabismus	15.1 (26)	Head turned: 65.4 (17) Head tilted: 34.6 (9)	50 (11/22)	Follow-up: 65.4 (17) Surgery: 34.6 (9)	Esotropia (61.5) Exotropia (38.5)	Fusion: 35.7 (5/14) Stereopsis: 87.5 (7/8)
Nystagmus blockage syndrome	4.1 (7)	Head turned: 85.7 (6) Combined: 14.3 (1)	100 (6/6)	Follow-up: 85.7 (6) Prism: 14.3 (1)	Orthotropia (57.1) Esotropia (28.6) Exotropia (14.3)	Fusion: 25 (1/4) Stereopsis: 100 (1/1)
Sixth nerve palsy	4.1 (7)	Head turned: 100 (7)	0 (0/6)	BT: 57.1 (4) Follow-up: 28.6 (2) Prism: 14.3 (1)	Esotropia (100)	Fusion: 0 (0/5) Stereopsis: 66.6 (2/3)
Extraocular muscle fibrosis	3.5 (6)	Chin down/up: 66.7 (4) Head turned: 16.7 (1) Combined: 16.7 (1)	100 (5/5)	Follow-up: 66.7 (4) Surgery: 16.7 (1) BT: 16.7 (1)	Exotropia (33.3) Vertical deviation (33.3) Esotropia (16.7) Esotropia + vertical deviation (16.7)	Fusion: 33.3 (1/3) Stereopsis: 100 (1/1)
Third nerve palsy	2.9 (5)	Head turned: 60 (3) Head tilted: 20 (1) Combined: 20 (1)	50 (2/4)	Surgery: 80 (4) Follow-up: 20 (1)	Exotropia (60) Vertical deviation (20) Exotropia + vertical deviation (20)	Fusion: 0 (0/3) Stereopsis: 66.6 (2/3)
Brown syndrome	1.7 (3)	Head tilted: 66.7 (2) Head turned: 33.3 (1)	0 (0/2)	Surgery: 66.7 (2) Follow-up: 33.3 (1)	Orthotropia (66.7) Vertical deviation (33.3)	Fusion: 0 (0/2) Stereopsis: 100 (1/1)
Oculocutaneous albinism	1.2 (2)	Head turned: 50 (1) Combined: 50 (1)	100 (2/2)	Follow-up: 100 (2)	Orthotropia (50) Esotropia (50)	Fusion: 50 (1/2) Stereopsis: 0 (0/1)
Heavy eye syndrome	0.6 (1)	Chin down/up: 100 (1)	100 (1/1)	Surgery: 100 (1)	Esotropia + vertical deviation (100)	Fusion: 0 (0/1) Stereopsis: 100 (1/1)

AHP: Abnormal head posture, BT: Botulinum toxin, n: Number of patients

Table 2. Changes in AHP by treatment method (n=94)

Treatment	Change in AHP, % (n)		
	AHP reduced	AHP resolved	AHP remained the same
Surgery (n=66)	77.3 (51)	16.7 (11)	6.1 (4)
Botulinum toxin (n=4)	50.0 (2)	25.0 (1)	25.0 (1)
Follow-up (n=24)	8.3 (2)	0 (0)	91.7 (22)

AHP: Abnormal head posture, n: Number of patients

Moreover, the most common AHP type in our study was head tilt, followed by head turn, combined, and chin down/up positions. This finding is similar to the frequency ranking of AHP types in the study by Erkan Turan et al.[5] In contrast, Akbari et al.[8] observed in their study that the predominant AHP type was head turn (48.3%), followed by head tilt (24.8%), combined (20.8%), and chin up (6%) positions.

Chin up or down head positions may develop due to orbital base fractures, thyroid myopathy, A-V pattern esotropia/exotropia, double elevator palsy, extraocular muscle fibrosis, congenital motor nystagmus, and congenital ptosis.[9] In our study, the chin down/up head position was the most common AHP type among patients with extraocular muscle fibrosis and heavy eye syndrome.

In nystagmus blockage syndrome, AHP occurs when the null point (the point where nystagmus is least noticeable and visual acuity is best) is not at primary gaze position. It can be variable but is often observed as the head turning away from the null point.[10] In our study, 85.7% of patients diagnosed with nystagmus blockage syndrome presented with head turn, whereas this rate was 25% in the study conducted by Erkan Turan et al.[5]

Patients with superior oblique palsy, which is one of the leading ocular causes of AHP, are expected to exhibit head tilt with chin down and ipsilateral head turn. However, some cases may present with only head tilt or only head turn.[3] Erkan Turan et al.[5] reported that 87.3% of patients with superior oblique palsy had head tilt, 3.6% had head turn, 7.3% had combined head tilt and turn, and 1.8% had a chin down position. Nucci et al.[11] reported that of 12 AHP patients with superior oblique palsy, 10 had head tilt and 2 had a combined head position. Similarly, the fourth cranial nerve palsy patients in our study mostly exhibited head tilt (90.7%), with head turn (7%), chin down/up (1.2%), and combined (1.2%) being less common AHP types.

The compensatory head posture is a motor adaptation developed to achieve binocular single vision.[12] The development of AHP may not be expected in the presence of amblyopia or suppression because AHP is a compensatory mechanism that occurs in patients whose fusion capacity and visual acuity are over a certain level.[13] In our study, 30.6% of the patients had fusion, 14.8% had diplopia, and 54.6% had suppression. However, similar to the study conducted by Erkan Turan et al.[5], no significant relationship was found between Worth 4-dot test results and amblyopia. In addition, the significant relationships between amblyopia and both diagnosis and AHP type demonstrated in our study emphasizes that amblyopia should be considered in diseases such as nystagmus blockage syndrome, oculocutaneous albinism, and extraocular muscle fibrosis. Although the relationship between AHP type and amblyopia was statistically significant, drawing a definitive conclusion may not be advisable due to the varying number of patients in the AHP groups.

Different treatments can be used to correct AHP, depending on the etiology and orthoptic examination findings. Teodorescu[1] explained the mechanism of AHP as "the head moves where the eye cannot, to avoid diplopia" and emphasized that an adequate surgical treatment can correct deviation, diplopia, and AHP. Zheng et al.[14] reported resolution of infantile nystagmus syndrome in 95% of patients at postoperative 1-3 weeks and resolution of AHP in 82% of patients at 2-year follow-up. Gündüz et al.[15] reported that AHP resolved postoperatively in all patients with Duane retraction syndrome, primary inferior oblique hyperfunction, and superior oblique palsy. In our study, we observed AHP reduction in 77.3% and resolution in 16.7% of patients treated surgically.

AHP may also develop to provide binocular vision and prevent diplopia in patients with congenital non-progressive Duane retraction syndrome, which is characterized by limitation of horizontal eye movements and globe retraction. Prism glasses or extraocular muscle surgery can be performed to correct the compensatory head position.[16] Surgery may also be useful in correcting cosmetically intolerable globe retraction and upward or downward displacement of the affected eye upon adduction.[17] In our study, AHP resolved or decreased in 8 of 12 patients with Duane retraction syndrome who underwent corrective surgery.

Study Limitations

Our study has the limitations inherent to retrospective research. In addition, some of the patients included in our study were too young for binocularity, stereopsis, and amblyopia assessment. The fact that some patients did not continue follow-up also resulted in the inability to observe their post-treatment change in AHP. A study with larger diagnostic groups can be conducted to obtain more detailed results.

Conclusion

AHP can be caused by many different conditions. The results of our study revealed a significant relationship between patients' AHP types and diagnoses, which suggests that a patient's AHP may provide clues to their diagnosis at first sight. However, conducting a detailed examination for amblyopia, binocular vision, and eye movement limitations is still essential. The association between amblyopia and both AHP type and diagnosis highlights the need to be vigilant for amblyopia depending on the patient's diagnosis and AHP type. Reduction or resolution of AHP was noted in most patients treated by surgery or botulinum toxin administration. In light of this information, it should be kept in mind that AHP can be modified with a correct diagnosis and the right treatment.

Ethics

Ethics Committee Approval: Ethics Committee of Ondokuz Mayıs University (decision no: OMÜ KAEK 2022/563, date: 28.12.2022).

Informed Consent: Retrospective study.

Declarations

Authorship Contributions

Surgical and Medical Practices: L.N.Ş., Concept: L.N.Ş., Design: L.N.Ş., B.E., Data Collection or Processing: B.E.,

Analysis or Interpretation: B.E., Literature Search: B.E., Writing: B.E.

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

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Original Article

Prevalence of Retinal Vascular Diseases in a Tertiary Care Hospital in Türkiye: A Hospital-Based Epidemiologic Study

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Abstract

Objectives: To determine the prevalence of diabetic retinopathy (DR), retinal vein occlusion (RVO), and retinal artery occlusion (RAO) in a tertiary care hospital in Türkiye.

Materials and Methods: The electronic records of all patients over the age of 18 years admitted to a tertiary care general hospital between January 2022 and January 2024 were retrospectively analyzed. For each of the three diseases, demographic data such as age, sex, and common complications were evaluated.

Results: A total of 140,344 patients were retrospectively analyzed. Of these patients, 44.6% (n=62,575) were male and 55.4% (n=77,769) were female. The number of patients diagnosed with retinal vascular disease was 1,963 and 52.3% (n=1,028) of these patients were female. The prevalence of retinal vascular diseases in the general population was 1.4% (95% confidence interval [CI]: 1.34% to 1.46%). The prevalence of DR, RVO, and RAO was 1.12% (95% CI: 1.07% to 1.18%), 0.27% (95% CI: 0.24% to 0.3%), and 0.01% (95% CI: 0% to 0.01%), respectively. Among these three diseases, DR was statistically more common in women (p=0.048) and RAO in men (p=0.015), while RVO (p=0.079) was not associated with sex. In patients with DR, macular edema was more common in patients older than 50 years, while neovascularization was more common in patients younger than 50 years. The development of macular edema and neovascularization was not associated with sex in patients with these three diseases.

Conclusion: This is the first study to report the demographic data of patients diagnosed with retinal vascular diseases in Türkiye. However, there is a need for nationwide, multicenter, hospital and community-based studies including different geographical regions of Türkiye that examine the data of patients in detail.

Keywords: Diabetic retinopathy, retinal vein occlusion, retinal artery occlusion, prevalence, macular edema, neovascularization

Introduction

Retinal vascular diseases are characterized by decreased retinal blood flow, leakage, exudation, ischemia, or neovascularization and induce changes such as retinal cell edema and atrophy.[1,2,3,4] Effective treatment is imperative to prevent transient or permanent vision loss. The retinal vascular diseases most commonly diagnosed in ophthalmology outpatient clinics are diabetic retinopathy, retinal vein occlusions, retinal artery occlusions, and hypertensive retinopathy. With early diagnosis and appropriate treatment of these diseases, vision loss can be minimized and organ damage avoided.[4,5,6]

Prevalence is the number of cases of a disease or condition present in a given population at a given time. Studies revealing the epidemiological characteristics of a population allow the prevalence of common diseases to be determined. By obtaining accurate information about the prevalence of diseases, health authorities can more clearly assess the health needs of a population, develop programs to prevent diseases, and ensure that resources are prioritized for the purpose of improving public health.

The aim of our study was to determine, for the first time in our country, the prevalence of diabetic retinopathy, retinal vein occlusion, and retinal artery occlusion (the most frequently diagnosed retinal vascular diseases in ophthalmology clinics) among patients presenting to a tertiary hospital, thus contributing to the protection of public health and the correct planning of health services and resources.

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Materials and Methods

This study was approved by the University of Health Sciences Türkiye, Ankara Training and Research Hospital Ethics Committee (ethics number: E-24-151, date: 06.06.2024) and conducted in accordance with the principles of the Declaration of Helsinki. Being a retrospective study, informed consent was not obtained.

We retrospectively reviewed the electronic records of all patients over the age of 18 years who presented to the Ophthalmology Outpatient Clinic of the University of Health Sciences Türkiye, Ankara Training and Research Hospital, a tertiary general hospital, between January 2022 and January 2024. Among these patients, the demographic data (e.g., age, sex, diagnosis) of patients diagnosed with diabetic retinopathy, retinal vein occlusion, or retinal artery occlusion and followed up in the retina outpatient clinic of our department were examined. The diagnostic criteria for the retinal vascular diseases are given below.

Patients who were diagnosed with diabetes mellitus and had retinopathy findings such as microaneurysm, dot hemorrhages, and soft or hard exudate on dilated fundus examination were designated as having diabetic retinopathy. The records of patients with diabetic retinopathy were retrospectively examined to determine whether they had macular edema, received intravitreal injection, developed proliferative diabetic retinopathy (PDR), and underwent panretinal photocoagulation.

Patients with dilated fundus examination findings such as intraretinal hemorrhages, occlusion and dilation of an affected vein, and presence of soft exudate were classified as retinal vein occlusion and further grouped as branch retinal vein occlusion or central retinal vein occlusion according to the occluded segment. For these patients, we retrospectively examined whether macular edema developed and whether intravitreal injection and panretinal photocoagulation were performed.

Patients whose dilated fundus examination showed occlusion of a retinal artery with ischemic whitening of the retina only along the course of the occluded branch were diagnosed as having branch retinal artery occlusion. If the ischemic whitening involved all four quadrants and was accompanied by a cherry-red spot, the patient was diagnosed as central retinal artery occlusion. We retrospectively examined demographic characteristics such as age and sex for patients who received these diagnoses and were followed in the retinal outpatient clinic.

Of the patients with diabetic retinopathy and retinal vein occlusion who developed macula edema, those who had a decline in visual acuity and evidence of macular edema on optical coherence tomography (Heidelberg Engineering, Franklin, MA, USA) were treated with intravitreal injections of ranibizumab (Lucentis®; Genentech/Roche, USA), aflibercept (Eylea®, Bayer, Berlin, Germany), bevacizumab (Altuzan®, Roche), or dexamethasone intravitreal implant (Ozurdex®; Allergan, Inc., CA, USA). Laser photocoagulation (Topcon Pascal Pattern Scanning Laser, Medical Laser Systems, Tokyo, Japan) was performed in patients who were diagnosed with these three retinal diseases and had signs of neovascularization in the retina, iris, or angle.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous data were expressed as mean ± standard deviation. Categorical data were expressed as number and percentage. Chi-square test and Fisher's exact test were used for univariate analysis. A p value <0.05 was considered statistically significant.

Results

The records of 140,344 patients who presented to the ophthalmology outpatient clinic of our hospital between January 2022 and January 2024 were retrospectively reviewed. Of these patients, 44.6% (n=62,575) were male and 55.4% (n=77,769) were female and the majority were between the ages of 18-29 and 40-69 years (n=108,080). The demographic data of these patients by age group and sex are shown in Figure 1.

A total of 1,963 patients were diagnosed with retinal vascular disease, and 52.3% (n=1,028) of these patients were female. The prevalence of retinal vascular diseases in the entire population was 1.4% (95% confidence interval [CI]: 1.34% to 1.46%). Of these 1,963 patients, 1,575 (80.2%) were diagnosed with diabetic retinopathy, 377 (19.2%) with retinal vein occlusion, and 11 (0.6%) with retinal artery occlusion. The prevalences of diabetic retinopathy, retinal vein occlusion, and retinal artery occlusion were 1.12% (95% CI: 1.07% to 1.18%), 0.27% (95% CI: 0.24% to 0.3%), and 0.01% (95% CI: 0% to 0.01%), respectively. Prevalence and demographic data of patients diagnosed with these retinal vascular diseases are given in Tables 1, 2 and Figures 2, 3.

Diabetic retinopathy was most common between the ages of 60-69 years (37%, n=579) and 50-59 years (26.4%, n=416) and was statistically more common in women (53%, n=834) (p=0.048). There was no difference between male and female patients in terms of age at diagnosis. Of the 1,575 patients diagnosed with diabetic retinopathy, 513 received intravitreal

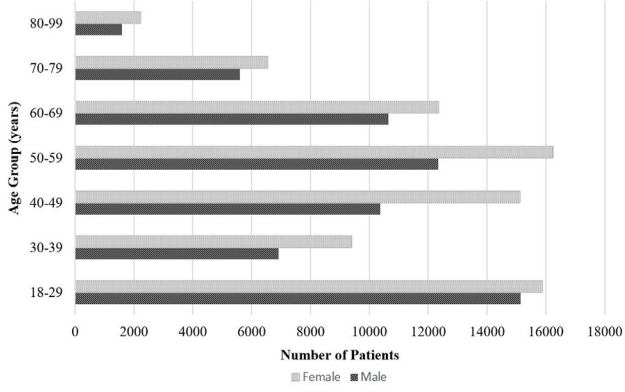

Figure 1. Distribution of all patients examined in the ophthalmology clinic, by age and sex

injection due to macular edema. The prevalence of macular edema in patients with diabetic retinopathy was 32.7% (95% CI: 30.26% to 34.89%). Patients who received intravitreal injections due to macular edema were most frequently between the ages of 60-69 years (36.2%, n=186), with no significant difference between females and males (p=0.173). There were 241 patients with diabetic retinopathy who underwent panretinal photocoagulation due to the development of PDR. Laser photocoagulation was most commonly required in patients aged 50-69 years, of which 129 were female and 112 were male. The prevalence of PDR among patients with diabetic retinopathy was 15.3% (95% CI: 13.52% to 17.08%). The rate of PDR did not differ between male and female patients (p=0.846) but was higher in patients under 50 years of age (p=0.002).

Of the 377 patients diagnosed with retinal vein occlusion, 192 (51%) were female and 185 (49%) were male. Vein occlusions were most common in the age ranges of 60-69 years (33%, n=123) and 70-79 years (26.5%, n=100). There was no difference between male and female patients in terms of age at diagnosis. Of these patients, 124 (32.9%) were diagnosed with central retinal vein occlusion and 253 (67.1%) with branch vein occlusion. Intravitreal injections for macular edema were administered to 198 of 377 patients diagnosed with vein occlusion. The prevalence of macular edema in patients with retinal vein occlusion was 52.52% (95% CI: 47.48% to 57.56%). Patients treated for macular edema were most frequently aged 60-69 years (34.3%, n=68), with no significant difference in injection according to sex (p=0.811). There were 25 patients who underwent panretinal photocoagulation due to the development of neovascularization. Laser photocoagulation was most often required in patients aged 60-79 years, and 10 of the patients who underwent laser treatment were female and 15 were male. The prevalence of neovascularization in patients with vein occlusion was 6.63% (95% CI: 4.12% to 9.14%). There was no significant sex difference in the development of neovascularization (p=0.348). Of the patients who developed neovascularization, 75% had central retinal vein occlusion.

There were 11 patients diagnosed with retinal artery occlusion, of whom 9 were male and 2 were female, and all were diagnosed with central retinal artery occlusion. None of the patients had branch retinal artery occlusion. Arterial occlusions were most common in the age range of 50-79 years (73%, n=8). However, the mean age was 75 years among female patients and 58.11 years among male patients. Panretinal photocoagulation was performed due to neovascularization in 2 (18%) of the 11 patients. The prevalence of neovascularization in patients with arterial occlusion was 18.18% (95% CI: -4.61% to 40.97%). There was no significant relationship between sex and the development of neovascularization (p=0.655). Comparisons of clinically significant macular edema (CSDME) and neovascularization development according to sex and age are shown in Table 3.

Table 1. Prevalence of retinal vascular diseases

Disease	Prevalence n (%, 95% CI)
All retinal vascular diseases	1963 (1.4, 1.34-1.46)
Diabetic retinopathy	1575 (1.12, 1.07-1.18)
Retinal vein occlusion	377 (0.27, 0.24-0.3)
Branch retinal vein occlusion	253 (0.18, 0.16-0.2)
Central retinal vein occlusion	124 (0.09, 0.07-0.1)
Retinal artery occlusion	11 (0.01, 0-0.01)

n: Number of patients, CI: Confidence interval

Figure 2. Distribution of retinal vascular diseases by sex

Table 2. Distribution of retinal vascular diseases by age and sex

	Diabetic retinopathy (n=1575)		Retinal vein occlusion (n=377)				Retinal artery occlusion (n=11)	
Parametre	**Female**	**Male**	**Female**		**Male**		**Female**	**Male**
n	834	741	192		185		2	9
Age, years (mean ± SD)	63.29±10.33	62.31±10.75	65.32±11.56		64.41±12		75±7.07	58.11±13.22
n			**VDT (n=253)**		**SRVT (n=124)**			
			Female	**Male**	**Female**	**Male**		
			132	121	60	64		
Age, years (mean ± SD)			60.6±9.58	63.9±8.6	62.52±5.06	64.52±9.46		
p*	**0.048**		0.079				**0.015**	

*Chi-square test, n: Number of patients, BRVO: Branch retinal vein occlusion, CRVO: Central retinal vein occlusion, SD: Standard deviation

Discussion

Retinal vascular diseases are common conditions that pose a threat to vision. Of these, diabetic retinopathy causes acute or chronic vision loss, while retinal vein and artery occlusions cause vision loss that can be acute and irreversible.[1,2,3,4] Therefore, calculating the prevalence of these diseases and their complications in the population is important to prevent both the individual (unemployment, permanent organ damage) and social losses (loss of labor, insurance costs) resulting from these diseases and the complications they cause. This large-scale, hospital-based study is the first to show the prevalence of diabetic retinopathy, retinal artery and vein occlusions, and the common complications of these diseases in Türkiye. In our study, the combined prevalence of these three retinal vascular diseases was 1.4%, with individual prevalence rates of 1.12% for diabetic

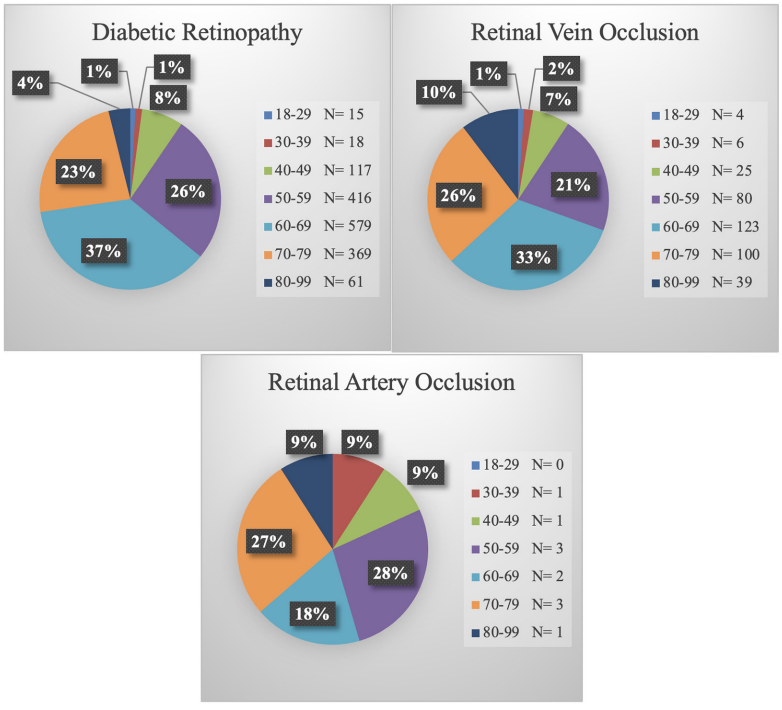

Figure 3. Distribution of retinal vascular diseases by age group

Table 3. Relationship between clinically significant macular edema and neovascularization development with age and sex

	Diabetic retinopathy (n=1575)		Retinal vein occlusion (n=377)		Retinal artery occlusion (n=11)	
	Female	**Male**	**Female**	**Male**	**Female**	**Male**
Clinically significant macular edema						
n	259	254	102	96		
Age, years (mean ± SD)	63.02±9.55	62.88±11.07	66.3±10.64	65.71±10.48		
<50 years**	23	28	6	6		
≥50 years**	236	226	96	90		
p*	0.173		0.811			
Neovascularization						
n	129	112	15	10		2
Age, years (mean ± SD)	59.38±10.2	60.03±10.35	67.13±11.54	62.8±10.8		55.5±0.71
<50 years	20***	17***	1	2		0
≥50 years	109	95	14	8		2
p*	0.846		0.348			

*Chi-square test (by sex), **Chi-square test (p>0.05 by age group), ***Chi-square test (p=0.002 in the diabetic retinopathy group by age subgroup), n: Number of patients, SD: Standard deviation

retinopathy, 0.27% for retinal vein occlusions, and 0.01% for retinal artery occlusions.

Looking at published studies on the prevalence of diabetes mellitus, a 2023 Turkish study examining the electronic records of 55,421,914 patients over the age of 14 years showed that 7,178,674 of these patients were diagnosed with diabetes mellitus and the prevalence of diabetes mellitus was 11.12%.[7] In terms of the global prevalence of diabetes mellitus, a study published in 2022 indicated that the global prevalence of diabetes in the 20-79 age group was 10.5% (536.6 million people) in 2021 and is predicted to increase to 12.2% (783.2 million people) by 2045.[8] The prevalence of diabetes mellitus in our country is similar to and even slightly lower than in other countries. When we examine studies on the prevalence of diabetic retinopathy, a study conducted in 2021 reported the prevalence of diabetic retinopathy as 3.95% in Taiwan and 15.9% in Korea.[9] In a large-scale study including 1,904,927 people in China, the prevalence of retinopathy among all patients admitted to hospitals between 2019 and 2021 was found to be 9.6% in 2019 and 10.3% in 2021.[10] Another Chinese study published in 2023 showed the prevalence of retinopathy among people with diabetes was 16.3%, with vision-threatening diabetic retinopathy having a prevalence of 3.2%.[11] A 2022 study from England showed that the prevalence of diabetic retinopathy in people over 18 years of age with diabetes decreased from 38.9% in 2012 to 36.6% in 2016.[12] In a 2024 study including people over 60 years of age in Iran, the prevalence of non-PDR was found to be 4.05%, while the prevalence of PDR was found to be 0.54%.[13] A 2021 meta-analysis examining the global prevalence of diabetic retinopathy indicated that the prevalence of diabetic retinopathy in people with diabetes was 22.27% overall and varied by region. The highest prevalence was in Africa (35.9%), the Middle East/North Africa (32.9%), and North America/Caribbean (33.3%), while the lowest prevalence was noted in South and Central America (13.37%).[14] In our study, the prevalence of diabetic retinopathy was calculated as 1.12% among all patients presenting to an ophthalmology outpatient clinic. This is lower than the prevalence reported in other countries. One reason for this may be that our study was hospital-based, and the diagnosed patients already had symptoms that affected their vision. As a result, our study may not have included patients with asymptomatic diabetic retinopathy. Another reason was that this study examined the prevalence of diabetic retinopathy among patients presenting to an ophthalmology outpatient clinic; if we had investigated the prevalence of diabetic retinopathy among people diagnosed with diabetes, we may have detected a higher rate.

If we examine the literature data regarding the relationship between diabetic retinopathy and age, a study conducted in China showed that diabetic retinopathy was most common in patients aged 45-60 years and second most common in those over 60 years of age.[11] In a study conducted in England, the mean age of patients with diabetic retinopathy was 65 years (54-75 years).[12] According to the aforementioned study on the global prevalence of diabetic retinopathy, the risk of developing diabetic retinopathy increased 2.41 times with each decade increase in age.[14] Similar to research conducted in other countries, diabetic retinopathy was most common in the 60-69 age group (37%) and second most common in the 50-59 age group (26.4%) in our study.

Regarding the relationship between diabetic retinopathy and sex, it was reported that female sex was associated with a high incidence of diabetic retinopathy in the study conducted in England, while the 2023 study conducted in China showed that women were less likely than men to have any diabetic retinopathy, vision threatening or not.[11,12] In another study examining the global prevalence of diabetic retinopathy, there was no relationship between sex and the development of diabetic retinopathy or diabetic macular edema, whereas sight-threatening diabetic retinopathy was seen more frequently among female than male patients.[14] In our study, females predominated among patients with diabetic retinopathy (53%) and the prevalence of diabetic retinopathy was statistically higher in female patients.

Diabetic macular edema is an important complication of diabetes that threatens vision, but the risk of vision loss can be reduced with early diagnosis and treatment. Looking at the literature data on the prevalence of diabetic macular edema, a study conducted in China showed that the prevalence of diabetic macular edema was 0.75%, while the prevalence of vision-affecting CSDME was 0.54%, and another study examining research from the USA and China indicated that the prevalence of CSDME was between 0.7% and 5.6%.[11,15] In the global prevalence study, regional differences in the prevalence of CSDME were observed (range, 2.30-6.06%), with an average of 4.07%.[14] In our study, the prevalence of CSDME requiring intravitreal injection therapy was 0.32%, slightly lower than reported in the literature, and there was no statistical difference between male and female patients in terms of the development of macular edema. Regardless of sex, the rates of intravitreal injection therapy were similar among patients under and over 50 years of age (34% vs. 32.5%). There was no sex-based difference in the need for intravitreal injection in patients in either age group.

In the literature, the prevalence of vision-threatening PDR was reported as 3.5% in the study conducted in England and 1.5-3.4% in the study examining data from the USA and China.[12,15] In a 2023 Chinese study, the prevalence of PDR was found to be 0.64%, whereas in the global prevalence study, prevalence was not evaluated separately for PDR but was calculated together with severe non-PDR and CSDME as sight-threatening diabetic retinopathy.[11,14] In our study, the prevalence of PDR was found to be 0.15% and was lower than in other studies in the literature, similar to the prevalences of diabetic retinopathy and CSDME.

When we examine the relationship between sex and the prevalence of CSDME and PDR, one of the studies conducted in China showed that women were less likely than men to have CSDME and vision-threatening diabetic retinopathy.[11] The study conducted in England also indicated that male sex was associated with higher risk of developing severe diabetic retinopathy and diabetes-related complications inversely to

age.[12] In the global prevalence study, sex had no effect on the development of CSDME and diabetic retinopathy, but the risk of developing vision-threatening diabetic retinopathy was slightly higher in women.[14] In our study, no sex-based differences were observed in the development of CSDME or PDR among all patients diagnosed with diabetic retinopathy, but laser therapy was required more frequently by patients under 50 years of age (25%) than those over 50 years of age (14.3%). When we examined patients under the age of 50 in terms of PDR development, a higher percentage of female patients required laser photocoagulation (29% vs. 21%) but there was no statistically significant difference between females and males. Laser photocoagulation rates among female and male patients over 50 years of age were similar (14.25% vs. 14.29%) but lower than in patients under 50 years of age.

Another common retinal vascular disease is retinal vein occlusions. When we look at the epidemiological data in the literature, a Chinese study determined the prevalence of retinal vein occlusions in people over the age of 18 in the years 2019-2021 was 0.73%, 1.13%, and 1.57%, respectively.[10] According to another study determining the global prevalence of retinal vein occlusions in the 30-89 year age group in 2019, the prevalences of retinal vein occlusion, branch retinal vein occlusion, and central retinal vein occlusion were found to be 0.77%, 0.64%, and 0.13%, respectively.[6] In a 2023 study conducted in Africa in patients over 30 years of age, the prevalence of retinal vein occlusion was found to be 0.8%, while another study reported the prevalences of branch and central retinal vein occlusions respectively to be 0.49% and 0.19% in patients over 60 years of age in Iran.[13,16] In our study, the prevalence of retinal vein occlusion, branch vein occlusion, and central retinal vein occlusion were 0.27%, 0.18%, and 0.09%, respectively. The prevalence of retinal vein occlusions in our study was relatively low compared to both global and national prevalences. Many authors have emphasized that high-sodium diets and hypertension are important etiological factors in the development of vein occlusion.[10] Therefore, the high salt consumption in China may explain the relatively higher prevalence of vein occlusion compared to other countries. In our study, systemic hypertension was present in 44% of patients diagnosed with retinal vein occlusion.

Regarding the impact of sex and age on retinal vein occlusion, a study conducted in China reported that the prevalence of vein occlusion was higher in patients over 50 years of age, but there was no relationship between sex and vein occlusion.[10] Similarly, in a study examining the global prevalence of vein occlusion, it was shown that the prevalence of vein occlusion increased with age (1.60 times higher risk of vein occlusion for every decade), but no relationship was found with sex.[6] In the African study as well, the rate of retinal vein occlusion was higher in people aged 50-69 years, but there was no relationship with sex.[16] Similar to other studies, the prevalence of vein occlusion increased with age but was not associated with sex among people over 60 in Iran.[13] In our study as well, there was no relationship between sex and the development of retinal vein occlusion, whereas the prevalence of vein occlusion increased with age. In our study, 60% of the patients diagnosed with vein occlusion were between 60 and 79 years of age.

When we look at studies examining the prevalence of macular edema or neovascularization, which are among the important complications of retinal vein occlusion, the prevalence of macular edema has been reported to be between 5-20%.[17,18] In our study, the prevalence of macular edema secondary to retinal vein occlusion and requiring treatment was 52%. We think that the high prevalence of macular edema in our study is due to the fact that our study was hospital-based and included patients presenting to the hospital due to symptoms such as decreased vision. When we look at the relationship between sex and age and the development of macular edema, no difference was found between the female and male sexes in terms of the need for intravitreal injection. In our study, the mean age of patients who received intravitreal injections was 66.02±10.54 years, and 94% of our patients were over 50 years of age. If we evaluate the development of neovascularization, 6.7% of our patients required photocoagulation and 75% of these patients had a diagnosis of central retinal vein occlusion. Other studies have also reported the rate of retinal neovascularization in central retinal vein occlusion as 5%.[19] In our study, no relationship was observed between sex and the need for laser therapy.

Another important retinal vascular disease is retinal artery occlusion. This acute pathology results in retinal ischemia and infarction, and requires urgent diagnosis and treatment.[4] Retinal artery occlusion has been reported in previous studies to have an incidence of 0.001-0.02% and be more common in men.[20] In a study examining the incidence of retinal artery occlusion before and after the coronavirus disease-2019 (COVID-19) pandemic, the rates were 0.6% and 0.7% for central retinal artery occlusion and 1.1% and 1.2% for branch retinal artery occlusion, respectively, with no difference before and after COVID.[21] In a study conducted in Korea, patients diagnosed with retinal artery occlusion in 2002-2018 were examined and the prevalence of retinal artery occlusion was found to be 0.007%.[22] In our study, the prevalence of retinal artery occlusion was found to be 0.01%. When we examined the relationship between sex and retinal artery occlusion, it was observed that 9 of the 11 patients diagnosed with arterial occlusion were male and 2 were female, consistent with other published studies in which arterial occlusion was seen more frequently in men. Of these 11 patients, 2 (18%) underwent laser photocoagulation due to the development of neovascularization. The rate of neovascularization after central retinal artery occlusion was similar to that reported in the literature (18.2%).[23]

Study Limitations

Firstly, as this study was hospital-based, it evaluated the prevalence of retinal vascular diseases among patients presenting

to the hospital as a result of symptoms. However, it will be useful as a pioneering work for future community-based studies that represent the entire population. Secondly, we analyzed the demographic data of the patients such as age, sex, and frequent complications, but not all systemic diseases, visual acuity, or detailed imaging findings. A more comprehensive analysis including these data would undoubtedly be useful.

Conclusion

In conclusion, our study is the first to report the prevalence of the most common retinal vascular diseases and their most common complications in Türkiye. The prevalence rates of diabetic retinopathy, retinal vein occlusions, and retinal artery occlusions respectively in our study were 1.12%, 0.27%, and 0.01%. We observed that the development of diabetic retinopathy was more common in women. In terms of the development of complications (macular edema and PDR), there was no difference between male and female patients, whereas patients under the age of 50 showed greater risk for PDR and those over the age of 50 were at higher risk for macular edema.

Although a higher percentage of male patients were diagnosed with retinal vein occlusion, there was no statistical difference according to sex. There was also no difference between the male and female sexes in terms of macular edema or neovascularization development. Laser photocoagulation was performed due to the development of neovascularization in 6.7% of our patients, 75% of whom were diagnosed with central retinal vein occlusion. Finally, the prevalence of retinal artery occlusion in our study was 0.01%. Retinal artery occlusion was more frequent in males, who also had a lower age at diagnosis than female patients.

Our study is the first to report the demographic data of patients diagnosed with retinal vascular disease in Türkiye. However, there is a need for both hospital- and community-based, multi-center studies examining more comprehensive patient data and including different geographic regions of Türkiye.

Ethics

Ethics Committee Approval: University of Health Sciences Türkiye, Ankara Training and Research Hospital Ethics Committee (ethics number: E-24-151, date: 06.06.2024).

Informed Consent: Retrospective study.

Declarations

Authorship Contributions

Surgical and Medical Practices: Ö.C., G.O., N.Ü., G.Ü., A.B., Concept: Ö.C., N.Ü., Design: Ö.C., G.O., N.Ü., G.Ü., A.B., Data Collection or Processing: Ö.C., G.O., Analysis or Interpretation: Ö.C., G.O., N.Ü., G.Ü., A.B., Literature Search: Ö.C., G.O., Writing: Ö.C., G.O., N.Ü., G.Ü., A.B.

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Original Article

Strabismus Accompanying Pediatric Cataracts and the Effect of Cataract Surgery on Strabismus

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Abstract

Objectives: To examine the characteristics of preoperative strabismus, the impact of surgical treatment on existing strabismus, and the features of strabismus developing postoperatively in pediatric cataract patients.

Materials and Methods: The records of patients who underwent surgery for pediatric cataract and had at least 1 year of follow-up were reviewed. Preoperative strabismus types, changes in strabismus after surgery, and the characteristics of postoperative new-onset strabismus were examined.

Results: Seventy-seven pediatric cataract surgery patients were evaluated, 58 (75.3%) with congenital cataract and 19 (24.7%) with acquired cataract. The mean follow-up duration was 63 months (range: 13-185 months). Cataracts were bilateral in 39 patients and unilateral in 38 patients. Strabismus was present preoperatively in 21% of unilateral cases and 20.5% of bilateral cases. In unilateral cases, 50% had esotropia (ET) and 50% had exotropia, while in bilateral cases, these rates were 75% and 25%, respectively. Orthotropia was achieved postoperatively for at least for 1 year of follow-up in 25% of patients with preoperative deviation, all of whom had ET. Twenty-nine (47.5%) of 61 patients who had no deviation preoperatively developed strabismus postoperatively. The rate of new-onset postoperative strabismus in patients with unilateral cataract was 91.6% for those operated before 1 year of age and 38.5% in those operated after the age of 1 year (p=0.001). For bilateral cases, these rates were 50% and 22.2%, respectively (p=0.155).

Conclusion: Strabismus development is commonly observed in pediatric cataracts. While preoperative strabismus may resolve after surgery, postoperative rates remain high, especially in unilateral cases operated before 1 year of age. When managing pediatric cataracts, it is important to carefully evaluate not only for deprivation amblyopia but also strabismic amblyopia. Long-term systematic follow-up after cataract surgery is essential for optimal visual outcomes

Keywords: Exotropia, esotropia, cataract surgery, pediatric cataract

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Introduction

Pediatric cataracts are one of the leading causes of treatable vision loss in childhood.[1,2] In addition to reducing vision, they also inhibit normal visual development, resulting in the development of strabismus, amblyopia, or nystagmus. While the incidence of strabismus in the general population ranges from 2-5%, it is more common in children who undergo cataract surgery, with reported rates ranging from 20.5% to 86%.[3,4,5,6,7,8,9] Concomitant strabismus is one of the main obstacles to achieving isometropia and binocular vision after successful cataract surgery.

The aim of this study was to examine the characteristics of preoperative concomitant strabismus, the effect of cataract surgery on existing strabismus, and its relationship with new-onset postoperative strabismus in pediatric cataract patients.

Materials and Methods

The medical records of patients who underwent surgery for pediatric cataract in the pediatric ophthalmology and strabismus unit of our clinic between 2000 and 2021 were examined retrospectively.

Children under 10 years of age who underwent surgery for unilateral or bilateral cataract and were followed up for at least 1 year were included in the study. Patients with traumatic cataract were excluded from the study, but those with a history of preterm birth and those with isolated ocular diseases such as persistent fetal vasculature were included. All surgeries were performed by the same surgeon (H.A.) using the same technique

(phacoemulsification/lens aspiration + posterior capsulotomy + anterior vitrectomy ± peripheral iridectomy ± intraocular lens implantation).

The patients' age, sex, follow-up period, laterality of cataract, type of cataract, preoperative and postoperative vision in evaluable cases, anterior segment and fundus examination findings, age at cataract surgery, presence and type of strabismus preoperatively and postoperatively, and intraocular lens implantation status were recorded from their records. In addition to total cataract, partial cataract was defined as nuclear, posterior subcapsular, and posterior polar cataract obscuring the optic axis and requiring surgery. Angle of deviation was measured with the Krimsky test in non-cooperative and very young patients and with the cover test and prism alternating cover test from a distance of 6 meters for far and 30 cm for near vision in the other patients. Changes in the patients' preoperative deviations and the characteristics of new-onset postoperative strabismus were evaluated.

This study was conducted in accordance with the principles of the Helsinki Declaration and ethics committee approval was obtained from the Ankara University Faculty of Medicine Ethics Committee (dated: 21/11/2023, decision no: İ10-712-23). Necessary permissions and informed consent forms were obtained from the patients' parents or legal guardians for the use of their information and images for scientific purposes.

Statistical Analysis

Mann-Whitney U test, Wilcoxon test, Pearson chi-square test, and Fisher exact test were used for statistical analysis. The cases with a p value <0.05 were considered statistically significant.

Results

The study included 77 patients who underwent surgery for pediatric cataract. Of these, 58 (75.3%) had congenital cataract and 19 (24.7%) had acquired cataract. The mean follow-up period was 63 months (range, 13-185 months). Forty-eight (62.3%) of the patients were male and 29 (37.7%) were female. Cataracts were bilateral in 39 patients (50.6%) and unilateral in 38 patients (49.3%). The mean age at surgery was 36.8 months (range, 1.5-120 months). Cataract surgery was performed at or before 1 year of age in 47 patients (61%), between 1 and 4 years of age in 16 patients (20.8%), and after 4 years of age in 14 patients (18.2%). All 58 (75.3%) patients with congenital cataract underwent cataract surgery before 3 years of age. Preoperatively, strabismus was observed in 16 patients (20.8%), while 61 patients (79.2%) did not have strabismus. The demographic data of patients with and without strabismus before cataract surgery are shown in Table 1. A total of 52 patients (67.5%) underwent intraocular lens implantation and 25 (32.5%) remained aphakic. Strabismus surgery was performed in 20 patients with an angle of deviation greater than 20 prism diopters, those with a fixation preference, or had suppression detected on Worth 4-dot test or stereopsis test.

Strabismus was present preoperatively in 8 patients (21%) with unilateral cataract and 8 patients (20.5%) with bilateral cataract. Of these unilateral cases, 50% had esotropia (ET) and 50% had exotropia (XT). Among the bilateral cases, these rates were 75% and 25%, respectively. Of the total 16 patients with preoperative strabismus, 4 (25%) exhibited orthotropia sufficient to eliminate the need for strabismus surgery after cataract surgery. One (6.25%) of these patients had unilateral cataract, 3 (18.75%) had bilateral cataracts, and all patients with orthotropia had ET as the preoperative deviation. Among the 12 patients (75%) who did not achieve orthotropia, there was no postoperative change in the preoperative deviation type.

Strabismus was observed postoperatively in 41 patients (53.2%). New-onset strabismus occurred postoperatively in 29 (47.5%) of the 61 patients with no deviation before cataract surgery. Preoperative and postoperative clinical characteristics are shown for all patients included in the study in Table 2 and for those who did not have strabismus preoperatively and developed strabismus postoperatively in Table 3.

The relationship between cataract laterality and age at surgery among the 29 patients who did not have preoperative strabismus and developed strabismus after cataract surgery is evaluated in Table 4. Strabismus developed in 91.6% of 12 unilateral cases who underwent cataract surgery before the age of 1 year, while this rate was 38.5% among the 18 patients who underwent cataract surgery after the age of 1 year. In bilateral cases, strabismus developed in 50% of 22 cases operated before 1 year of age and 22.2% of 9 patients operated after 1 year of age. When patients with unilateral cataract and those with bilateral cataract were compared amongst themselves according to the timing of surgery, the development of new-onset strabismus was more common in unilateral cataract when surgery was performed in the first year of life (p=0.001), while there was no significant relationship between surgical timing and strabismus development in bilateral cases (p=0.155).

Discussion

Our study showed that 47.5% of pediatric cataract patients developed postoperative new-onset strabismus after cataract surgery, but strabismus present before surgical treatment could be corrected after cataract surgery in 25% of patients. Analysis of the relationship between surgical timing and postoperative strabismus development revealed no relationship in bilateral cases, whereas in unilateral cases, the frequency of strabismus increased in patients who underwent cataract surgery within the first year of life. ET was observed to be more common in bilateral cases both preoperatively and postoperatively. However, despite nearly equal numbers of unilateral and bilateral cases and preoperative strabismus rates, the prevalence of strabismus postoperatively was markedly higher in unilateral cases postoperatively (60.5% vs. 47.4%).

It is known that strabismus frequently accompanies pediatric cataract. In the literature, the frequency of this association ranges from 20.5% to 86%.[5,6,7,8,9] In our study, this rate was found to be 20.8%, which is among the lower values in the literature data. The lower rate of strabismus in our study may be explained by

Table 1. Examination of demographic data and cataract characteristics in patients with and without preoperative strabismus			
	Preoperative strabismus	**No preoperative strabismus**	**Total**
Patients, n (%)	16 (20.8)	61 (79.2)	77 (100)
Sex F/M, n (%)	5 (6.5)/11 (14.3)	24 (31.2)/37 (48)	29 (37.7)/48 (62.3)
Mean age at diagnosis months (range)	8.2 (3-29)	8.5 (1-36)	8.4 (1-36)
Mean follow-up time months (range)	77.9 (13-149)	59.1 (13-185)	63 (13-185)
Cataract type, n (%)			
Congenital	13 (16.9)	45 (58.4)	58 (75.3)
Acquired	3 (3.9)	16 (20.8)	19 (24.7)
Cataract laterality, n (%)			
Unilateral	8 (21)	30 (79)	38 (49.4)
Bilateral	8 (20.5)	31(79.5)	39 (50.6)
Extent of cataract, n (%)			
Total	4 (16)	21(84)	25 (32.5)
Partial	12 (23.1)	40 (76.9)	52 (67.5)
Nystagmus	5 (29.4)	12 (70.6)	17 (22.1)
n: Number of patients, F: Female, M: Male			

Table 2. Preoperative and postoperative clinical characteristics of all patients in the study			
	Number of patients n (%)	**Frequency of strabismus n (%)**	**Strabismus type n (%)**
Preoperative cataract laterality	77 (100)	16 (20.8)	
Unilateral	38 (49.4)	8 (21)	4 (50) ET, 4 (50) XT
Bilateral	39 (50.6)	8 (20.5)	6 (75) ET, 2 (25) XT
Postoperative cataract laterality	77 (100)	41 (53.2)	
Unilateral	38 (49.4)	23 (60.5)	11 (47.8) ET, 12 (52.2) XT
Bilateral	39 (50.6)	18 (47.4)	12 (66.7) ET, 6 (33.3) XT
n: Number of patients, ET: Esotropia, XT: Exotropia			

Table 3. Clinical characteristics of patients without preoperative strabismus who developed strabismus postoperatively			
	Number of patients n (%)	**Frequency of strabismus n (%)**	**Strabismus type n (%)**
Cataract laterality	61 (100)	29 (47.5)	
Unilateral	30 (49.1)	16 (53.3)	8 (50) ET, 8 (50) XT
Bilateral	31 (50.2)	13 (41.9)	9 (69.2) ET, 4 (30.8) XT
n: Number of patients, ET: Esotropia, XT: Exotropia			

Table 4. Relationship between cataract laterality and timing of surgery in patients without preoperative strabismus who developed strabismus after cataract surgery (n=29)			
	Frequency of strabismus		
Age at surgery (years)	**≤1 year**	**>1 year**	**p**
Cataract laterality			
Unilateral	11/12 (91.6%)	5/18 (38.5%)	**0.001**
Bilateral	11/22 (50%)	2/9 (22%)	0.155

the low mean age at surgery and the difficulty in identifying and measuring the angle of preoperative deviations in affected patients due to cataract.

Studies evaluating the frequency of preoperative strabismus separately in unilateral and bilateral cataract have yielded strikingly different results.[10,11,12] Tartarella et al.[10] reported the prevalence of preoperative strabismus as 47.3% in bilateral and 52.7% in unilateral cases. In contrast, Awner et al.[11] determined the frequency of preoperative strabismus to be 29% in unilateral cases, while O'Keefe et al.[12] reported this rate as 30% in bilateral cases. Although these studies indicated that strabismus was more common in unilateral than bilateral pediatric cataract, Kong et al.[13] reported that their rates were similar. In our study, the frequency of strabismus did not differ between unilateral and bilateral cases, as in the study by Kong et al.[13]

In terms of the relationship between cataract laterality and the frequency of strabismus development after cataract surgery, there are many different studies in the literature.[6,9,11,14,15] The incidence of postoperative new-onset strabismus in unilateral cataract was reported as 60.7% by Bothun et al.[14] and 75% by Lambert et al.[6] In bilateral cataract, the frequency of postoperative strabismus was reported by Lee and Kim[9] as 17.2% and by Park et al.[15] as 55.4%. In our study, this rate was found to be 53.3% in unilateral cases and 41.9% in bilateral cases. Differences between studies may be related to the characteristics of the selected patient group. Factors such as age at cataract diagnosis, age at cataract surgery, cataract type and laterality, and surgical technique are thought to impact the incidence of strabismus.

Several studies have also reported different results regarding the type of strabismus seen in pediatric cataracts.[7,8,14,15,16,17,18,19] Demirkilinc Biler et al.[16] found that ET was more common in postoperative follow-up in both unilateral (66.7%) and bilateral (68.6%) congenital cataract patients without strabismus in the preoperative period. Similarly, other studies also demonstrated that ET was more common in the presence of congenital cataracts.[7,8,14,17,18] France and Frank[5] reported that unilateral congenital cataract patients had approximately equal rates of ET and XT, whereas ET was more common in bilateral cases. On the other hand, Park et al.[15] and Weisberg et al.[19] reported that XT was more common than ET. In our study, both types of strabismus were observed at approximately equal rates preoperatively and postoperatively in unilateral cataract cases, while in bilateral cases, ET was observed more frequently, at rates of 75% preoperatively and 66.7% postoperatively. Spanou et al.[17] reported that ET was more common in congenital cases. As most of the cases in our study had congenital cataract, ET was found to be more common in bilateral patients. Ethnic characteristics may also be a factor in the higher incidence of ET.

Looking at the effect of pediatric cataract surgery on existing deviation, David et al.[20] reported that 32.3% of patients with strabismus before cataract surgery became orthotropic. Kong et al.[13] found that 72% of 54 pediatric cataract patients with strabismus at the time of diagnosis exhibited orthotropia after cataract surgery. In both studies, at least 1-year follow-up data were examined for both unilateral and bilateral pediatric cataract. In our study, we observed that orthotropia was achieved for at least 1 year after surgery in 25% of the cases with strabismus preoperatively. In all patients with orthotropia, the deviation was ET. In cataract patients with strabismus at baseline, it is more appropriate to treat the cataract before strabismus and make decisions about strabismus surgery after cataract treatment.

Regarding the relationship between strabismus development and the timing of cataract surgery, most studies have shown that strabismus occurred more frequently in children who underwent early cataract surgery than late surgery.[9,15,21,22] David et al.[20] reported that age at surgery was the main risk factor for developing strabismus. In their study, strabismus developed in 80% of patients with unilateral cataract and 64.29% of bilateral patients who underwent surgery before 36 months of age. Park et al.[15] detected strabismus in 51.6% of bilateral cases operated before 12 months. In contrast, Magli et al.[23] reported that the age at cataract diagnosis and age at surgery were not significantly associated with strabismus. In our study, the prevalence of strabismus among patients who underwent surgery at or before 1 year of age was 91.6% among unilateral cases and 50% among bilateral cases. For patients operated after the age of 1 year, the prevalence of strabismus was lower, at 38.5% in unilateral cases and 22% in bilateral cases. The reason for this may be that patients operated earlier have greater cataract density, and the resulting deprivation has a more negative effect on binocular vision development. In addition, the higher rate of postoperative strabismus despite early surgery among cases operated at 1 year or earlier suggests that visual rehabilitation may not have been adequately implemented due to these patients' young age.

Conclusion

As a result, strabismus development is common in pediatric cataract. Despite successful surgical treatment, strabismus occurs at a high rate in the postoperative period, especially in unilateral cases operated within the first year of life. This increases the risk of cataract-related deprivation amblyopia as well as strabismus-related suppression and amblyopia.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the principles of the Helsinki Declaration and ethics committee approval was obtained from the Ankara University Faculty of Medicine Ethics Committee (dated: 21/11/2023, decision no: İ10-712-23).

Informed Consent: Obtained.

Declarations

Authorship Contributions

Surgical and Medical Practices: H.A., Concept: G.G.B., N.R., P.B.K., H.A., Design: G.G.B., N.R., P.B.K., H.A., Data Collection or Processing: G.G.B., N.R., Analysis or Interpretation: G.G.B., N.R., P.B.K., H.A., Literature Search: G.G.B., Writing: G.G.B.

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Strategies for Sustainability and Cost Optimization in Corneal Transplantation: From Surgeons' Perspective

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Abstract

The main purpose of this review is to provide an overview of surgical strategies that can be implemented in keratoplasty to maximize resource utilization and enhance sustainability. To achieve this, we conducted a thorough search of PubMed to identify articles on sustainability and cost-effectiveness in surgical settings, as well as studies comparing the cost-effectiveness of different keratoplasty techniques. Our review shows that both penetrating keratoplasty and lamellar techniques are cost-effective. However, lamellar techniques offer greater long-term sustainability and cost efficiency in addition to improving patient vision. For corneal transplantation surgeries, strategies such as reducing operating room time, properly educating the surgical team, reusing instruments like trephines and punches, using surgical materials economically, and selecting the appropriate surgical technique are recommended to enhance sustainability and reduce costs. The strategies outlined could contribute to more sustainable practices in keratoplasty procedures. In conclusion, although ensuring the economical use of surgical materials is beneficial for improving sustainability and reducing costs during surgery, utmost care should be taken to preserve safety and effectiveness while taking measures to reduce costs, and a balance should be achieved between sustainability and patient safety.

Keywords: Cornea, keratoplasty, sustainability

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Introduction

"The life of every child born today will be profoundly affected by climate change. Without accelerated intervention, this new era will come to define the health of people at every stage of their lives." -Lancet Countdown 2019 report.[1]

Climate change is recognized as one of the greatest threats to global health in the 21st century.[2] The health sector is known to contribute significantly to the production of greenhouse gas emissions, with a report published in 2019 stating that health sector-related emissions accounted for at least 4.4-5.0% of all global greenhouse gas emissions.[3] To highlight the significant contribution of the health sector to carbon emissions, it has been emphasized that if global health care were a country, it would be the fifth largest contributor to carbon emissions.[4] Ophthalmology, which differs from other branches in that it has rapid patient circulation and the highest number of surgeries in the health system, may constitute a substantial part of this burden.

Penetrating keratoplasty has been regarded as the most commonly used procedure in corneal transplant surgery since it was first performed by Eduard Zirm in 1905.[5] This technique is successful, safe, and effective, and many innovations and advances have been achieved in this field in recent years. Worldwide, the demand for corneal transplantation has been reported as approximately 12.7 million patients. However, it is estimated that this number may be even higher due to problems such as underreporting and limited access to health care in developing countries.[6]

The main cost drivers in penetrating keratoplasty are often the length of hospital stay, recurrent outpatient visits, and visual rehabilitation procedures.[6] Additional costs arise from the preparation, proper storage, and transportation of donor corneas. In addition, the choice of surgical technique can also play an important role in reducing costs and ensuring sustainability. To date, however, there has been no publication in the literature

evaluating from the surgical perspective with the aim of reducing keratoplasty costs and contributing to sustainability.

Careful planning and precautions are necessary ensure a sustainable future and the appropriate allocation of resources. Therefore, the main objective of this review is to provide an overview of surgical strategies that can be implemented in keratoplasty surgeries to maximize resource utilization and increase sustainability.

Penetrating Keratoplasty: Is it a Cost-effective Surgical Procedure?

In many publications in the literature, it has been clearly demonstrated that penetrating keratoplasty is considered a cost-effective surgical procedure and complies with the threshold value found in the World Health Organization's definition of cost-effective interventions.[5,6,7] Hirneiss et al.[5] evaluated the cost-effectiveness of penetrating keratoplasty in patients with poor binocular visual acuity and reported that penetrating keratoplasty was cost-effective, despite being an expensive procedure during the operation. Considering graft survival in the 10-year postoperative period, they determined a cost utility of 11,557 USD per quality-adjusted life year. As visual acuity is the main criterion considered when determining the ophthalmological benefit, it can be assumed that a patient with poor visual acuity in one eye and good visual acuity in the other eye will benefit less from penetrating keratoplasty than a patient with poor binocular visual acuity. However, Hirneiss et al.[5] emphasized that despite good visual acuity in the fellow eye in preoperative assessment, performing penetrating keratoplasty in the treatment of the eye requiring transplantation surgery is still quite cost-effective.

Reducing Costs and Contributing to Sustainability in the Operating Room

The basic strategy for sustainability can be summarized as the 5R rule (reduce, reuse, recycle, rethink, and research). All of these principles can be applied to keratoplasty procedures.

1. Reduce

Reducing Operative Time

It is a well-known fact that longer operative times lead to higher costs. A review published by Wu et al.[8] examined the importance of a surgical team consisting of well-trained personnel. The authors emphasized that an experienced team could significantly reduce operative times, thereby lowering costs. Another study analyzed the effect of preparing a preoperative checklist on operating room turnover time and costs.[9] It was determined that preoperative checklists resulted in the faster provision of necessary surgical instruments in the operating room and reduced operating room usage time and surgical costs.

Reducing Energy Consumption and Plastic Waste

Energy consumption can be reduced by turning off lights when the operating room is not in use and turning off devices when not needed. With current technology, timers and motion detector systems can also help save energy in the operating room.[10]

One of the most important sources of waste is the plastic packaging used to store surgical instruments and devices (Figure 1). In addition to being harmful to the environment, such disposable plastic packaging incurs serious costs.[11] Instead of packing single-use surgical equipment individually, packing in batches containing appropriate gloves and disposable gowns may be a useful way to reduce waste associated with plastic packaging. In addition, single-use sterile packs often contain unnecessary items not used in the surgical procedure. Revising these packs and reducing unnecessary items can contribute to improving sustainability.

Cunningham et al.[12] evaluated 113 surgical procedures in their 12-day pilot study and determined that 46 items were unnecessarily included in surgical packs. In the same study, the results of a 3-week follow-up and evaluation of 359 surgical procedures indicated potential savings of 1,111.88 USD by eliminating unnecessary items from surgical packs. In the continuation of the study, removing unnecessary items from surgical packs over the course of 1 year resulted in savings of 27,503 USD.[12]

The "do not open what you will not use" principle should be the main viewpoint for ophthalmological surgeons.

Single Cornea, Multiple Surgeries

Another option to both solve the high demand for keratoplasty and increase sustainability may be to use a single donor corneal tissue for multiple lamellar surgeries such as deep anterior lamellar keratoplasty (DALK) and Descemet membrane endothelial keratoplasty (DMEK). In a study by Siddharthan et al.[13], this method was reported to be successful and safe, and may allow corneal surgeons in developing countries to more sustainably meet the demand for keratoplasties without the need for expensive tools such as a microkeratome. Opting to use a single donor cornea for multiple lamellar procedures, such as both DALK and DMEK, may be a sensible way to meet the high demand for keratoplasty as well as improve sustainability.

2. Reuse

In keratoplasty procedures, many surgical instruments such as trephines and corneal punches that are marketed by manufacturers as single-use can be reused in corneal transplantation. In addition, studies have reported that sterile marking pens and rulers provided in plastic packaging can be reused with a negligible risk of infection.[14]

There is no study examining the reuse of disposable products made for single use in various ophthalmological surgeries. However, in a study evaluating gynecological operations, the reuse of disposable devices was reported to yield similar efficacy and safety when compared to single use.[15]

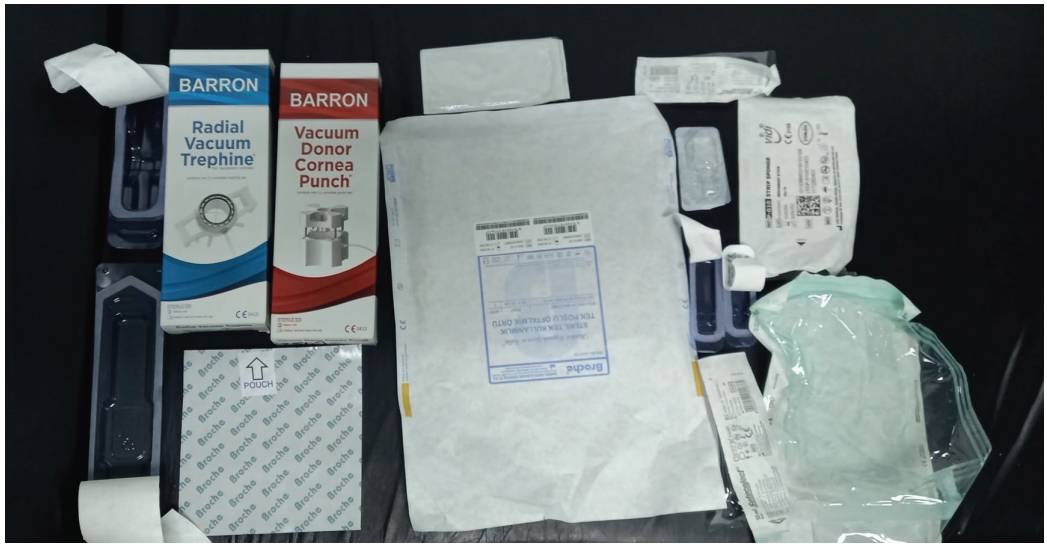

Figure 1. Plastic and paper waste generated during preparation for keratoplasty

Manatakis and Georgopoulos[16] evaluated the impact of reusing instruments in laparoscopic patients compared to single-use products and determined that costs were 9 times higher with single-use products. The authors emphasized that in urology or gynecology departments, choosing to reuse would allow an additional 50-100 procedures per year to be performed for the same cost. In addition to significantly reducing costs, no safety-related issues were reported with reusable laparoscopic instruments. Moreover, the maintenance costs arising from reusable devices and tools were found to be acceptable. In another study, Kwakye et al.[17] reported that using reusable surgical gowns instead of disposable gowns reduced carbon-producing waste by 23,000 kg and saved 60,000 USD per year.

Although there are conflicting views on the energy and water costs of cleaning and sterilizing reusable products, many studies have shown that reusable devices have a lower carbon footprint than single-use devices, and the sustainability benefits of choosing reusable products have been reported in various publications.[18,19] Tool reuse might be expected to cause more technical problems compared to single-use tools. However, these problems can be overcome with technological advances, new and more durable designs, and appropriate staff training. For example, both trephines and corneal punches can be reused several times without sharpening and can be replaced after several surgeries. On the other hand, scissors can be used longer and may require sharpening after 60 to 80 surgeries.

3. Recycle

Waste separation and recycling is another important way to improve sustainability as well as benefit economically.[20] McGain et al.[21] reported that recycling does not add any additional costs and that the impact might be greater if recycling were widely adopted by the global health system. Most operating room waste consists of recyclable material such as paper or plastic packaging, metal, or glass.[22,23] The positive impact of recycling on the economy or environment may seem low on an individual basis, but if implemented globally, recycling can be a very useful way to ensure sustainability in health care.

4. Rethink

Rethinking the Economical Use of Surgical Supplies

During surgery, there are several ways to reduce costs associated with surgical supplies as well as increase sustainability. For example, cutting the suture close to the knot while suturing can be an effective way to prevent suture waste and complete the surgery using half of the suture material in a package. Using the remaining suture in the next corneal transplantation may be an effective way to reduce costs. Using both sides of the absorbent cotton swabs frequently used during surgery, increasing the number of surfaces by cutting the sticks into smaller pieces, and trying to use less viscoelastic material are other useful ways to contribute to sustainability and reduce costs. Optimizing cleaning and sterilization methods is essential to make the sterilization of reusable devices cost-effective and sustainable. Unnecessary sterilization procedures should also be avoided.[24]

Education and Awareness

Standardization of surgical training in ophthalmology is another way to improve sustainability and cost-effectiveness. A recent study indicated that experienced surgeons had better outcomes in terms of surgical success and were more cost-effective than less experienced ones.[25] Greater surgical experience may reduce the complication rate, resulting in a decrease in

complication costs. Training programs related to ophthalmology should also provide information on invoicing processes, effective and equitable distribution of resources, and cost reduction strategies. A study by Ross et al.[26] showed that simple education such as cost awareness posters for surgeons in operating rooms resulted in a significant increase in the reuse of single-use surgical instruments.

To summarize, rethinking involves educating and motivating ophthalmologists to minimize cost and improve sustainability. It can also be considered a reminder of the need to be careful about unnecessary sterilization procedures. Reducing operating room usage time for corneal transplantation procedures, properly educating ophthalmologists and the surgical team, reusing instruments such as trephines and corneal punches, attempting to use surgical supplies more economically, and choosing the appropriate surgical technique are all possible beneficial ways to improve sustainability and reduce costs during surgery.

5. Research

Further research should be conducted to understand the carbon footprint of various ophthalmological procedures, including keratoplasty, and to develop solutions. There is only one study evaluating the carbon footprint associated with keratoplasty surgeries, in which Borgia et al.[27] reported that endothelial keratoplasties involve a significant carbon footprint. However, more comprehensive supportive studies are needed.

Which Keratoplasty Technique Should Be Preferred?

Penetrating Keratoplasty versus DALK

Penetrating keratoplasty has been the standard surgical procedure of choice for corneal transplantation for many years.[28] It is a safe and effective procedure, although graft failure is a complication seen in 10-34% of patients.[29,30] The main causes of graft failure are endothelial rejection and endothelial failure. To overcome these complications, lamellar transplantation techniques have been developed. These surgeries involve transplantation of the anterior cornea only.

Without intervention to the endothelium, the risk of endothelial rejection or endothelial cell loss is reduced. In DALK, the corneal stroma is excised down to Descemet's membrane. However, the procedure is technically challenging.[27] A study conducted by van den Biggelaar et al.[31] showed that DALK was more costly than penetrating keratoplasty in the first postoperative year. As their study evaluated only the first postoperative year, it can be argued that long-term cost analyses may yield different results.

Cost differences in the comparison of DALK and penetrating keratoplasty may be related to the time-consuming "large bubble technique" in DALK, which increases operating room time compared to penetrating keratoplasty. However, the potential endothelial complications and need for retransplantation that may occur after penetrating keratoplasty may lead to higher costs in the long term compared to DALK. Therefore, the cost-effectiveness of DALK could increase over time, and longer follow-up studies are needed.

Penetrating Keratoplasty versus Descemet Stripping Automated Endothelial Keratoplasty

Although penetrating keratoplasty has long been the standard technique for endothelial corneal diseases, it has several disadvantages such as suture-related complications, wound healing problems, and longer visual rehabilitation time.[32] Therefore, endothelial keratoplasty procedures have increased in popularity in recent years. These procedures target endothelial transplantation only, with no intervention to the anterior of the healthy cornea. The main advantages of endothelial keratoplasty over penetrating keratoplasty include faster postoperative visual rehabilitation, lower-grade changes in astigmatism, better tectonic stability, and fewer suture-related complications.[33,34] Descemet stripping automated endothelial keratoplasty (DSAEK) is a technique in which the donor cornea is prepared using a microkeratome.[35]

There are several studies in the literature comparing DSAEK and penetrating keratoplasty in terms of cost-effectiveness. Short-term results in the literature have generally indicated that DSAEK is more costly. In the study by van den Biggelaar et al.[36], DSAEK was found to be more costly in the short term compared to penetrating keratoplasty. The two main sources of early costs of DSAEK are the preparation of donor tissue using a microkeratome and the use of an additional insertion apparatus when performing the surgery. In addition, procedure-specific complications such as graft detachment can require an additional operation, which further increases costs.[37] However, studies have shown that the frequency of graft detachment decreases rapidly with increasing surgeon experience.[38]

On the other hand, Bose et al.[7] evaluated the cost-effectiveness of both procedures based on values obtained 3 years postoperatively. Taking into account the initial fees for the surgical procedure and complication costs, the estimated average 3-year costs were 7476 USD for DSEK and 7236 USD for penetrating keratoplasty. Both penetrating keratoplasty and DSAEK were determined to be "very cost-effective" interventions according to the World Health Organization cost-effectiveness criteria. However, the authors clearly emphasized that although both surgeries meet the threshold set by the World Health Organization, DSAEK should be the preferred procedure if the goal is to increase health gains with stable resources.

In another study conducted in India, it was reported that DSAEK was significantly more costly than penetrating keratoplasty at postoperative 6 months.[39] However, analysis at postoperative 1 year showed that penetrating keratoplasty more costly than DSAEK, and DSAEK emerged as significantly more cost-effective at postoperative 2 years.

When comparing DSAEK and penetrating keratoplasty in terms of long-term cost-effectiveness, it should be noted that high astigmatism contributes substantially to the increase in

costs associated with penetrating keratoplasty. Contact lenses or glasses may be used for visual rehabilitation in patients, while additional surgery may be planned to reduce astigmatism in some cases. As postoperative astigmatism is expected to be significantly lower after DSAEK, lower costs related to astigmatism correction can also be expected. In addition, faster recovery after DSAEK accelerates patients' return to productivity, possibly contributing to the reduction of DSAEK-related costs in the long term. Moreover, the lower incidence of complications such as suture-associated infectious keratitis, shorter postoperative drug use, and the need for fewer outpatient visits may also contribute to reducing the cost of DSAEK procedures in the long term.

DSAEK versus DMEK

DMEK is an endothelial keratoplasty technique that enables transplantation of Descemet's membrane and endothelium without involving the posterior stroma. As this technique is performed through a smaller incision, more successful results are obtained both in terms of refraction and the increase in visual acuity. In addition, lower rates of endothelial rejection have been reported compared to DSAEK and penetrating keratoplasty.[40] The main disadvantage of this method is the long learning curve.[41] Many studies in the literature have reported that the DMEK procedure more effectively preserves endothelial cell function and can yield more successful visual results. Furthermore, endothelial rejection rates were found to be lower compared to DSAEK.[42,43]

In terms of cost-effectiveness, a study by Simons et al.[44] showed that DMEK was more costly compared to DSAEK in the short term (1 year). However, the increase in visual acuity was observed to be higher in the DMEK group. In contrast, Gibbons et al.[45] compared the long-term cost-effectiveness of DMEK and DSAEK and reported that DMEK was less costly than DSAEK.

In the study by Simons et al.[44], the long learning curve required for DMEK surgery may have been a contributor to the higher short-term cost, as the main source of the cost in the procedure was determined to be the need for additional rebubbling and graft placement due to lack of experience. On the other hand, studies based on longer-term results reveal that the cost difference decreases as the surgeon's experience with the DMEK technique increases. Revisions and precautions in DMEK surgery such as choosing SF_6 gas instead of air, creating a larger descemetorhexis, marking the graft to prevent orientation problems, and improving grafting techniques may reduce the rate of additional rebubbling.[46]

Complications that may develop in DSAEK, such as late graft failure or graft rejection, may affect the results in short-term cost-effectiveness analyses. Price et al.[47] evaluated 5-year graft survival rates in their study and found that graft rejection rates were higher in DSAEK patients than in the DMEK group.

In conclusion, when DSAEK and DMEK are compared, the long learning curve required for DMEK surgery may be a contributing factor to its higher cost in short-term analyses, because rebubbling and regrafting due to lack of experience were found to be the main sources of cost. However, higher graft rejection and lower graft survival rates in DSAEK patients may play a role in its higher costs compared to DMEK in the long term.

Conclusion

Reducing unnecessary costs is an important part of improving health system quality. However, the utmost care should be taken to preserve safety and effectiveness when implementing cost-reduction measures. In corneal transplantation surgeries, reducing operating room time, properly educating ophthalmologists and the surgical team, reusing instruments such as trephines and punches, striving for the economical use of surgical supplies, and choosing the appropriate surgical technique are all potential ways to improve sustainability and reduce costs during surgery. Further research is needed to improve this area of medicine and increase sustainability, and the tips and strategies presented in this review may contribute to a more sustainable world.

Declarations

Authorship Contributions

Surgical and Medical Practices: M.P., Concept: M.P., P.K., Design: P.K., Data Collection or Processing: P.K., Analysis or Interpretation: M.P., P.K., Literature Search: P.K., Writing: P.K.

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Review

Imaging in Pachychoroid Disease

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Abstract

The term pachychoroid was proposed as a term indicating an abnormal increase in choroidal thickness. Eyes presenting with pachychoroid changes often exhibit dilation of the large choroidal vessels, compressing the overlying choriocapillaris and Sattler's layer. Pachychoroid spectrum diseases may present pathological findings such as pigment epitheliopathy, choroidal neovascularization (CNV), submacular serous detachment, and distinct choroidal and scleral alterations. Recent advancements in imaging modalities such as widefield indocyanine green angiography (WF-ICGA), optical coherence tomography angiography (OCTA), and enhanced depth imaging optical coherence tomography (OCT) have significantly improved our understanding of these conditions. WF-ICGA revealed venous outflow congestion in the peripheral retina as one of the characteristics of pachychoroid diseases. Scleral thickness measurements using ultrasound biomicroscopy and anterior segment OCT indicate that a thicker anterior sclera may contribute to choroidal congestion and disease pathogenesis. OCTA has emerged as a superior tool for identifying CNV and understanding the disease etiology, offering better sensitivity and specificity compared to traditional methods. These imaging advancements provide valuable insights into the structural and functional changes associated with pachychoroid diseases, potentially guiding future diagnostic and therapeutic strategies. The aim of the present review is to define the morphological characteristics of the pachychoroid spectrum of diseases, which share similar choroidal findings.

Keywords: Pachychoroid disease, indocyanine green angiography, imaging, optic coherence tomography angiography, optic coherence tomography, scleral thickness

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Introduction

Pachychoroid diseases are a group of clinical entities defined by a thickened choroid and sharing common underlying pathological mechanisms. These include central serous chorioretinopathy (CSC), polypoidal choroidal vasculopathy (PCV), pachychoroid pigment epitheliopathy (PPE), pachychoroid neovasculopathy (PNV), and focal choroidal excavation (FCE). Peripapillary pachychoroid syndrome (PPS) and peripheral exudative hemorrhagic chorioretinopathy (PEHCR) are two additional pathologies recently included in the spectrum. These pathologies can overlap somewhat, and even evolve from one entity to another.

Pachychoroid disease can be visualized through enhanced depth imaging optical coherence tomography (EDI-OCT) or swept source (SS)-OCT. It is characterized by a thickened Haller choroidal layer (exceeding 300 µm), thinning of the Sattler and choriocapillaris layers, and dilated and hyperpermeable vessels.[1] These vascular changes can disturb Bruch's membrane and cause retinal pigment epithelium (RPE) alteration, resulting in serous retinal detachment with or without subsequent choroidal neovascularization (CNV).[1] Furthermore, indocyanine green angiography (ICGA) and optical coherence tomography angiography (OCTA) enable detailed visualization of blood flow within the retinal and choroidal vasculature.

Nearly a decade since the term was introduced, a universal agreement on the definition of pachychoroid remains unclear, with some authors consolidating disease entities while others prefer separate analyses.[2] Current diagnostic criteria for pachychoroid include: (1) reduced fundus tessellation, (2) pachyvessels (dilated outer choroidal vessels causing attenuation/thinning of other choroidal layers) observed on OCT and ICGA, (3) absence of soft drusen (total area of >125-µm circle) except for pachydrusen, defined as irregular yellow-white deposits

distributed across the posterior pole, and (4) presence of CSC characteristics including choroidal vascular hyperpermeability, RPE abnormalities independent of macular neovascularization, or a history of CSC.[2]

The pathogenesis of pachychoroid remains unclear, but different theories include steroid metabolism and vortex vein congestion. Mineralocorticoid receptors are expressed in the choroid, and their activation can lead to increased choroidal thickness (CT) and congestion, which may explain why stress is a major risk factor for CSC.[3] Congestion or blockage in the vortex veins has also been theorized to underlie pachychoroid spectrum disorders.[1,4,5] Venous drainage from the choroid mainly occurs through large vortex veins that drain blood from the choroid into the sclera. Congestion in vortex venous blood flow is believed to cause these veins to dilate due to heightened venous pressure, resulting in the retrograde flow of blood into neighboring quadrants through existing anastomoses.[6] Increasing pressure can ultimately damage the choriocapillaris layer, giving rise to these conditions.

Pachychoroid disease is still not fully understood and remains an active area of research. However, with recent technological advancements, our understanding of these conditions continues to improve.

Optical Coherence Tomography

Recent technological advancements such as EDI-OCT and SS-OCT have significantly enhanced our ability to visualize choroidal structures and elucidate the change in CT associated with pachychoroid disease.

Choroidal Thickness

It is not merely the thickness of the choroid itself, but more so the increased diameter of larger choroidal vessels that contributes to the overall increase in CT.[3] Healthy eyes with unusually thick choroids may be described as having "pachychoroid" or "uncomplicated pachychoroid".[3] To diagnose pachychoroid disease, it is necessary to identify pathological signs resulting from the dilation of choroidal vessels.

Utilizing EDI-OCT or SS-OCT, the choroid-scleral interface is traceable in the majority of eyes, enabling quantitative analysis of CT.[3] CT varies widely, with a subfoveal CT >300 µm generally considered pathological.[3] In conditions such as PCV, thicknesses ranging from 223 to 590 µm have been seen.[7] Increased CT is primarily due to vessel dilation in Haller's layer, visible as larger hyporeflective lumens on cross-sectional OCT, specifically in patients with CSC, PCV, FCE, and PPS.[8,9] En-face OCT and ICGA reveal that pachyvessels do not taper off towards the posterior pole but end abruptly, making them distinguishable from normal choroidal vessels.

Additionally, regional variations in CT show that the area beneath the fovea is thickest, while the nasal regions are thinnest.[10] In severe cases, Haller's layer vessels can occupy the entire thickness of the choroid. Even with normal or decreased CT, pachychoroid disease may be present if there is a decrease in inner choroidal volume due to atrophy. Therefore, assessing morphology with the help of automated software that analyzes the proportion of choroidal vascular luminal area to the total choroidal area, known as the choroidal vascularity index (CVI), is essential for diagnosis.

Choroid Vascularity Index/Choroidal Vascularity Index Map

While CT is a valuable measure, it only measures the total choroidal vasculature without differentiating between the stromal and luminal vascular component.[11,12] Therefore, Agrawal et al.[13] proposed the CVI as a novel OCT parameter. CVI provides a quantitative assessment of choroidal vascularity by determining the proportion of the choroidal vascular luminal area relative to the total choroidal area. This measurement enables comparisons between healthy eyes and those in different stages of pachychoroid disease.[12] The CVI map divides the choroid into vascular luminal and stromal areas, visually representing the choroidal vascularity across the posterior pole of the eye. Areas of higher vascularity appear brighter or denser, while areas with lower vascularity appear darker or less dense.[14,15] Studies have proposed using an Early Treatment Diabetic Retinopathy Study (ETDRS) grid-based method to measure CVI in the OCT scans of healthy subjects.[15] Shadow compensation and contrast enhancement techniques were included to improve OCT scan quality. The CVI was mapped across different regions of the macula according to the ETDRS grid, indicating that central macular CVI was lower compared to other quadrants in healthy subjects.[15] Although this analysis was restricted to the macular area, this new approach for CVI mapping with shadow compensation could contribute to a better understanding of various chorioretinal diseases, including pachychoroid diseases.

Agrawal et al.[13] examined CVI in the subfoveal choroidal area of eyes with CSC and fellow eyes and reported a higher CVI in the affected eyes. Increased CVI indicates greater choroidal vascularity in patients with acute CSC. In a more recent study, Sahoo et al.[14] found no significant difference in CVI values when comparing eyes with CSC, fellow eyes, and healthy controls using OCT. However, they did observe a rising CVI towards the macular center in CSC eyes. The most significant effect was observed in the subfoveal choroid, which showed a significant increase in choroidal luminal area. The higher CVI in this region suggests that subfoveal choroidal vessels are more reactive to stimuli than those in the rest of the choroid. Additionally, CT and CVI showed a positive correlation in CSC eyes, meaning that areas with a thicker choroid exhibited increased choroidal vascularity. This implies that stromal expansion and vascular dilation in CSC eyes are distributed unevenly, which may be a reflection of different responses to stimuli.[14]

Further studies comparing steroid-associated CSC and idiopathic CSC revealed that eyes with steroid-induced CSC had significantly higher CVI than those with idiopathic CSC.[16] The theory is that glucocorticoids may induce vascular dilation by binding to mineralocorticoid receptors in the choroidal vascular endothelium, thereby increasing CVI. Lower CVI eyes may have choroidal alterations, such as choroidal ischemia, which may be a helpful indicator of CNV risk in CSC.[14]

A large study comparing eyes with PCV to those with age-related macular degeneration (AMD) found that PCV was associated with a thicker baseline CT and a larger luminal choroidal area than AMD.[17] Therefore, CVI could be a practical measure for differentiating patients with AMD and PCV. Furthermore, CVI has been shown to be useful in distinguishing between two subtypes of PCV: those with choroidal vascular hyperpermeability (higher CVI) and those without (lower CVI).[17]

In order to distinguish between various pachychoroid conditions such as uncomplicated pachychoroid, PPE, PNV, CSC, and PCV, Demirel et al.[18] established cut-off levels for CVI. The CVI cut-off points were 72.7 for PPE versus PCV, 74.7 for PNV versus CSC, 72.6 for PNV versus PCV, and 73.6 for CSC versus PCV. These cut-offs help better understand the distinctions among these diseases. However, optimizing algorithms for CVI remains challenging, as research has indicated that factors such as blood, subretinal fluid, and pigment epithelial detachment (PED) can impact signal strength within the choroid, especially in eyes with PCV, CSC, and PNV.[17]

Imaging Use in Specific Conditions

Central Serous Chorioretinopathy

OCT has accurately depicted the dimensions and extent of serous neurosensory and pigment epithelium detachments associated with CSC. Although CSC was first identified using fluorescein angiography, RPE leakage in eyes with acute CSC has also been observed using OCT (Figures 1 and 2). Maltsev et al.[19] utilized en-face OCT images from OCTA to pinpoint

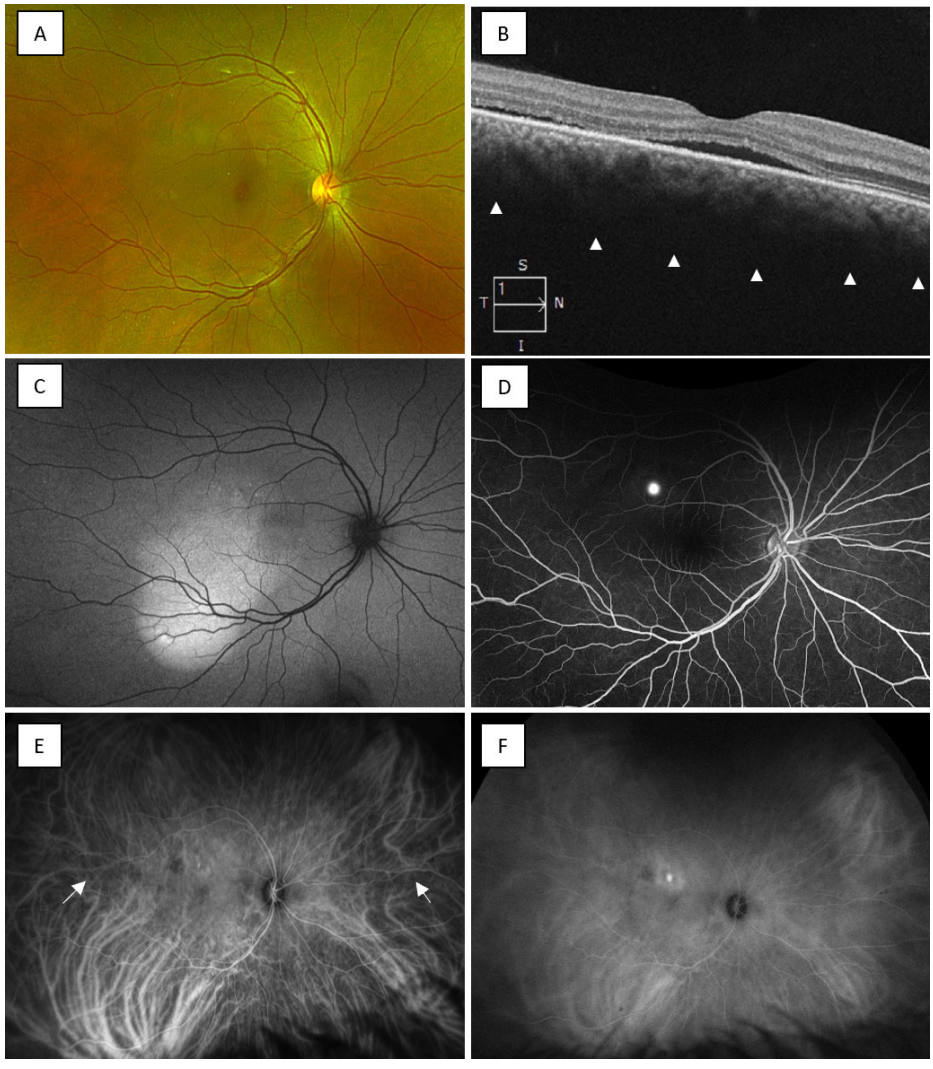

Figure 1. Multimodal imaging in central serous chorioretinopathy (CSC). A) Color fundus photograph of a 24-year-old female with CSC in the right eye. B) Optical coherence tomography scan through the fovea shows the presence of subretinal fluid, retinal pigment epithelium alterations, and pachychoroid (white arrow heads). C) Fundus autofluorescence shows the presence of hyperautofluorescent changes. D) Fluorescein angiography reveals a hyperfluorescent spot in the superotemporal parafoveal region. E) Early indocyanine green angiography (ICGA) shows the presence of choroidal vascular dilation and inter-vortex vein anastomoses (white arrows). F) Late ICGA shows a hypercyanescent spot in the superotemporal parafoveal region and multiple areas of hyperpermeability

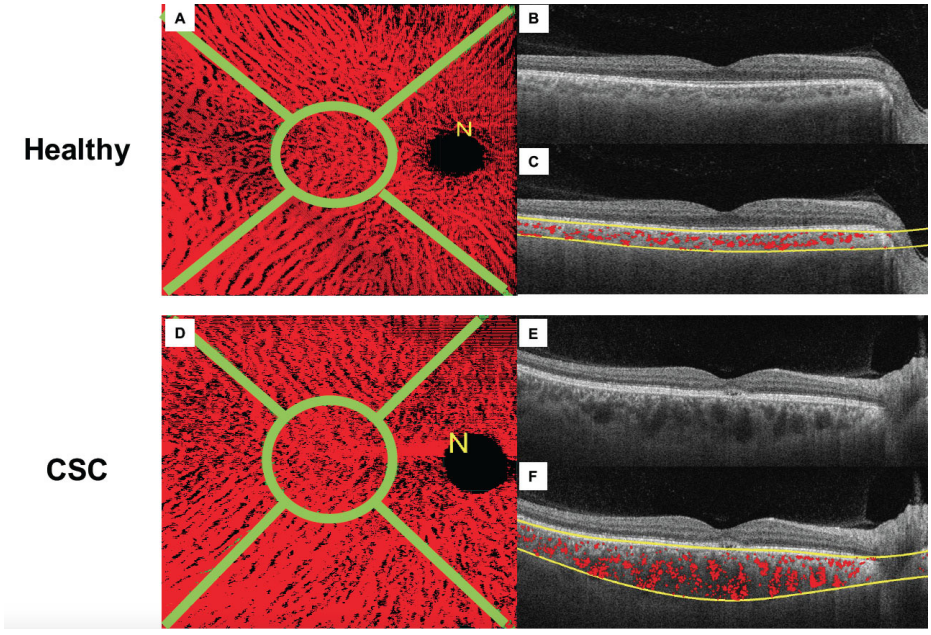

Figure 2. Three-dimensional (3D) reconstruction of the choroidal vessels in a healthy eye and an eye with central serous chorioretinopathy (CSC). A) 3D choroidal vessel map in a healthy 45-year-old man. B, C) Optical coherence tomography (OCT) B-scan and choroidal binarization, respectively. D) 3D choroidal vessel map in a 53-year-old man with CSC in the right eye. E) OCT B-scan showing subretinal fluid under the fovea. F) Choroidal binarization

the confirmed leakage point in 54.2% of CSC patients, eliminating the need for fluorescein angiography.

Individuals with CSC have a thicker choroid in all subfields compared to healthy eyes, as evidenced by EDI and SS-OCT (Figure 1). This increased thickness spans from the subfoveal region to peripheral areas, along with notable dilation of the veins within Haller's layer.[20] While cross-sectional OCT imaging shows increased CT in CSC patients, no corresponding changes are seen on ICGA. This disparity suggests a potential limitation of ICGA in capturing specific choroidal morphology alterations associated with CSC.[11,21] In contrast, the three-dimensional visualization provided by SS-OCT allows for more effective characterization of distinct retinal and choroidal layers. Additionally, the focal and diffuse choroidal dilations seen in en-face SS-OCT images align with hyperfluorescent areas on ICGA. These particular morphological changes in the choroidal vasculature that are visualized through en-face SS-OCT remain undetectable in conventional cross-sectional OCT images. Thus, en-face imaging emerges as an optimal modality for visualizing these features.[11]

OCT has been able to identify clinical characteristics that differentiate acute from chronic CSC. While both present with serous retinal neuroepithelial detachment, acute CSC shows serous retinal detachment that is primarily localized to the macular area and significantly elevated. In contrast, chronic CSC displays shallower detachment depths and more extensive detachment, often extending beyond the macular area or being multifocal.[22] Ruiz-Medrano et al.[23] also compared acute and chronic CSC findings using EDI-OCT and discovered hyperreflective spots and hyperreflective choroidal vessels but with varying prevalence: 83.3% and 75% in chronic CSC, compared to 33% and 6.7% in acute CSC, respectively. Ferrara et al.[11] investigated the effectiveness of en-face SS-OCT in identifying retinal and choroidal vasculature in patients with CSC, without the use of ICGA. At the level of the RPE, all eyes showed no signal corresponding to RPE detachment or loss, suggesting that the layer of cells nourishing the retina was intact. Enlarged vessels at the choriocapillaris level were present in more than 50% of the eyes. Furthermore, focal and diffuse choroidal dilation in Sattler's and Haller's layers were observed just beneath the area of RPE abnormalities, suggesting a potential relationship between choroidal changes and RPE abnormalities.[11] Overall, these findings suggest that en-face SS-OCT can identify choroidal and retinal neovascularization without the need for ICGA.

In their abovementioned study, Sahoo et al.[14] mapped CVI in patients with unilateral CSC using the ETDRS grid. The authors indicated that the outer nasal CT was significantly lower than both the central and inner nasal CT. Additionally, a positive correlation between CVI and CT was identified in CSC eyes, while this relationship was slightly weaker in fellow eyes and absent in healthy eyes. Generally, CSC eyes demonstrated an upward trend of CVI towards the macular center and superiorly, while fellow and healthy eyes exhibited a downward trend towards the macular center.[14]

Polypoidal Choroidal Vasculopathy

PCV, or pachychoroid aneurysmal type 1 CNV (PAT1), was first described by Yannuzzi et al.[24] in 1982. It is characterized by multiple serosanguineous detachments of the RPE and neurosensory retina, accompanied by secondary leakage from a branching vascular network.[25,26] The term PCV describes the appearance of branching choroidal vessels with terminal, polyp-like aneurysmal dilations.[24] While ICGA has traditionally been considered essential for diagnosing PCV, OCT findings are more accessible and have shown a strong correlation with ICGA findings in various studies (Figure 3).[27,28,29,30,31]

OCT has shown remarkable sensitivity and specificity in distinguishing between PCV and neovascular AMD.[32,33] Furthermore, the evaluation of color fundus photographs and OCT images together has proven to be quite accurate in differentiating PCV from CSC, as well as between PCV and AMD.[34]

A 2019 study assessed the diagnostic potential of certain features identified through fundus photography, OCT, and fluorescein angiography individually and combined for diagnosing PCV without ICGA.[35] The results showed that the presence of at least two out of four highly indicative features detected using fundus photography and OCT had 95% sensitivity and specificity for diagnosing PCV. These highly suggestive features include a notched or hemorrhagic PED on fundus photography, a sharply peaked PED at an angle of 70° to 90° on OCT, a notched or multilobulated PED on OCT, and a PED with underlying hyperreflective ring on OCT.[35] However, the study focused on untreated eyes, which poses a limitation and casts doubt on the applicability of the findings to treated eyes.

Pachychoroid Neovasculopathy

PNV, a term introduced by Pang and Freund[36], describes a distinct maculopathy where CNV emerges amidst areas of CT and dilation of choroidal vessels. There is continuing debate about whether PNV and AMD are distinct entities or part of a progression, and they can be mistaken for each other due to similarities in the blood vessel patterns observed.[37] Diagnosis has been challenging, particularly with techniques like fluorescein angiography, but OCT and OCTA offer clear imaging for accurate diagnosis. Key OCT biomarkers for PNV include a flat, irregular PED and the double-layer sign, which refers to visibility of the RPE and Bruch's membrane (Figure 4).[38,39,40] However, distinguishing between non-aneurysmatic PNV and aneurysmatic PAT1/PCV has become

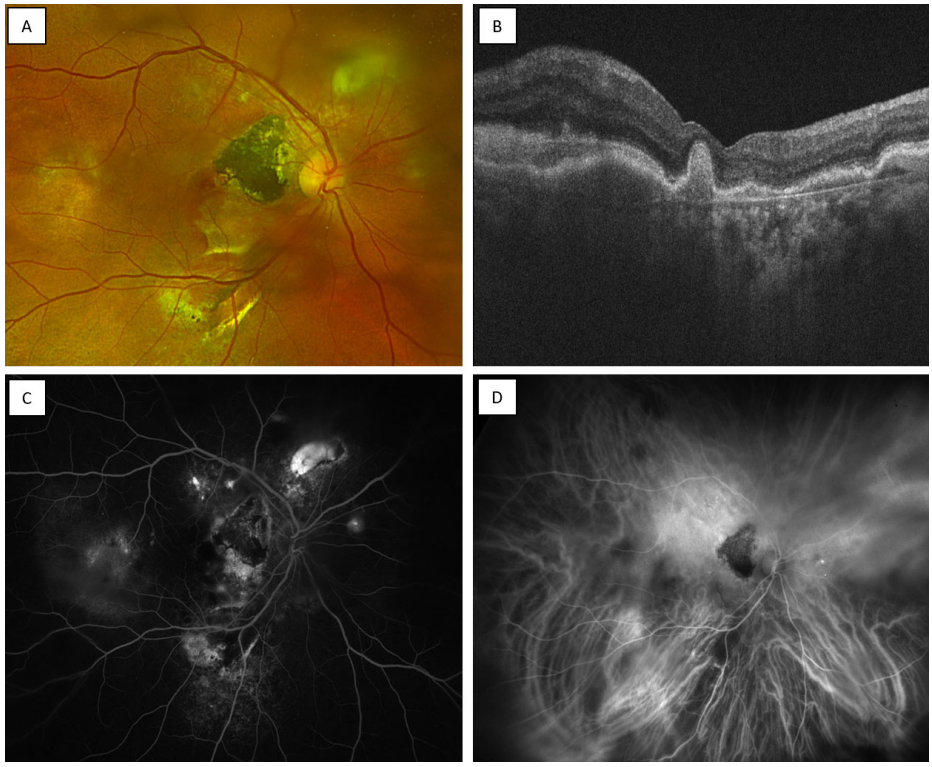

Figure 3. Multimodal imaging in polypoidal choroidal vasculopathy. A) Color fundus photograph of the right eye of a 64-year-old man. Note the retinal scars with the surrounding suprachoroidal hemorrhage in the peripapillary region. B) Optical coherence tomography scan through the fovea shows a complete alteration of the foveal profile. C) Fluorescein angiography shows the presence of hyper- and hypofluorescent areas in the macula and peripapillary region. D) Indocyanine green angiography shows the presence of dilated choroidal vessels, hyperpermeability, and hypercyanescent spots corresponding to the polypoidal lesions

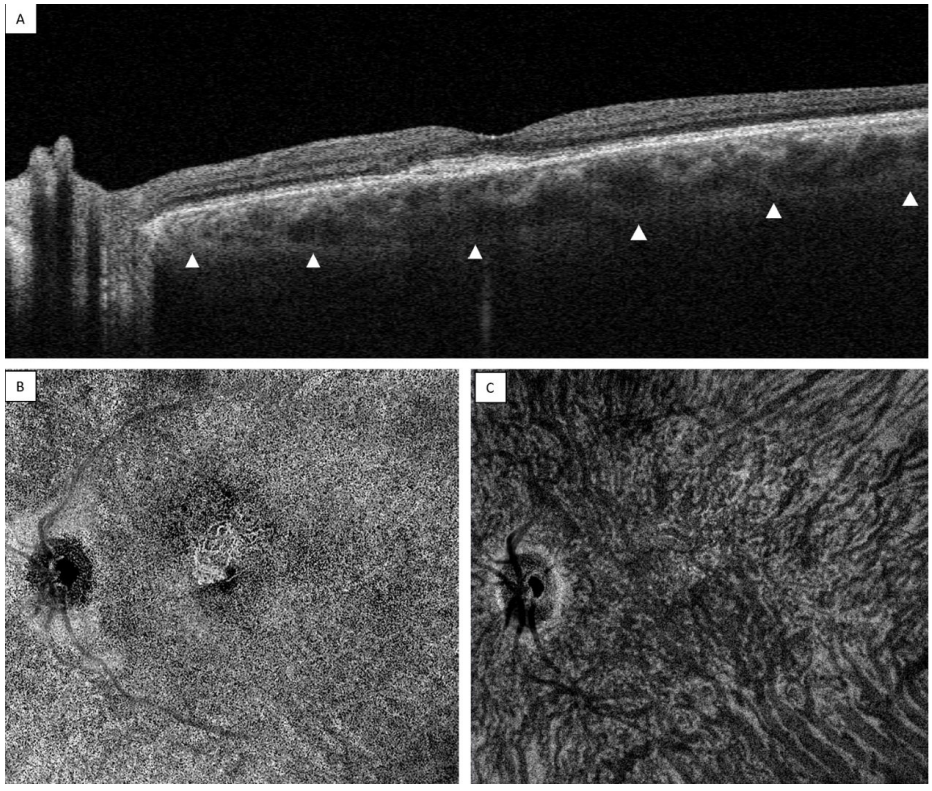

Figure 4. Optical coherence tomography (OCT) and OCT angiography (OCTA) in pachychoroid neovasculopathy. A) OCT scan through the fovea shows the presence of a flat, irregular pigment epithelium detachment (PED) in the subfoveal region. Note the pachychoroid (white arrow heads). B) En-face OCTA shows the presence of a choroidal neovascularization corresponding to the flat, irregular PED on OCT. C) En-face OCTA at the level of the choroid shows the presence of dilated choroidal vessels in the macula

increasingly complex and may be underappreciated due to the growing recognition of PNV as a new diagnostic entity.

Recent studies suggest that a significant portion of eyes diagnosed with PNV may have the aneurysmal form of pachychoroid neovascularization (PAT1/PCV).[41] Although ICGA is typically used for diagnosing PAT1/PCV, OCT is more widely available and can aid in diagnosis, especially in settings where ICGA is not accessible.[41] Given these circumstances, establishing a more precise set of diagnostic criteria for PAT1/PCV on OCT has become crucial to enhance clinical care. Specific OCT features, such as PED height, subretinal hyperreflective material above the PED peak, sub-RPE fluid, and hyperreflective material localized to the subretinal space are strong indicators of PAT1/PCV.[42] These findings underscore the importance of utilizing OCT alongside other imaging techniques, such as ICGA, for accurate diagnosis and differentiation between PNV and PAT1/PCV.

Pachychoroid Pigment Epitheliopathy

PPE is defined by RPE changes in pachychoroid eyes without the presence or history of subretinal fluid or soft drusen.[43] It is considered a form fruste of CSC, as the range of RPE abnormalities is similar to those found in CSC.[3] Karacorlu et al.[44] classified PPE into four types: RPE elevation with microbreak appearance, PED, RPE thickening, and hyperreflective RPE spikes.

Using SS-OCT and SS-OCTA, researchers have gained a deeper understanding of the relationship between choroidal vascular hyperpermeability observed with ICGA, choriocapillaris flow density, and CT in eyes with PPE. These advanced OCT technologies have revealed decreased choriocapillaris flow density, increased CT, and the co-localization of choroidal vascular hyperpermeability in PPE eyes.[45] Specifically, a 15% reduction in choriocapillaris flow density was observed in the quadrants affected by choroidal vascular hyperpermeability compared to the unaffected quadrants in the same eye. This finding suggests that despite CT, vascular hyperpermeability, and venous dilation (indicating higher choroidal blood flow and vessel congestion), there is ischemia in the inner choroid, RPE, and outer retina due to decreased choriocapillaris vascularity.[45] The advent of SS-OCT angiography has significantly improved choriocapillaris imaging compared to fluorescein angiography and ICGA.

Focal Choroidal Excavation

FCE is a concavity in the choroid of unknown etiology, occurring without any adjacent scleral abnormality or ectasia. This condition progresses slowly, with good visual acuity maintained over time with minimal changes. Jampol et al.[46]

first described this in 2006 using time-domain OCT. In 2010, Wakabayashi et al.[47] reported unilateral choroidal excavation using spectral-domain (SD)-OCT, which provided more detailed visualization of retinal and choroidal structure than time-domain OCT. SS-OCT uses an even longer wavelength than SD-OCT, allowing for better visualization of the choroid.[48] Overall, OCT is particularly important for its ability to provide detailed images of the retinal structure.[49,50,51]

Peripapillary Pachychoroid Syndrome

PPS, described by Phasukkijwatana et al.[9] in 2017, is characterized by a thick and hyperpermeable choroid in the peripapillary area and nasal macula. This choroidal congestion causes fluid accumulation within the retina and beneath the retina around the optic nerve, leading to a crowded appearance of the optic disc, choroidal folds, and occasionally optic disc edema (Figure 5).[52] OCT scans can detect intraretinal fluid in both the nasal and temporal regions near the optic discs, along

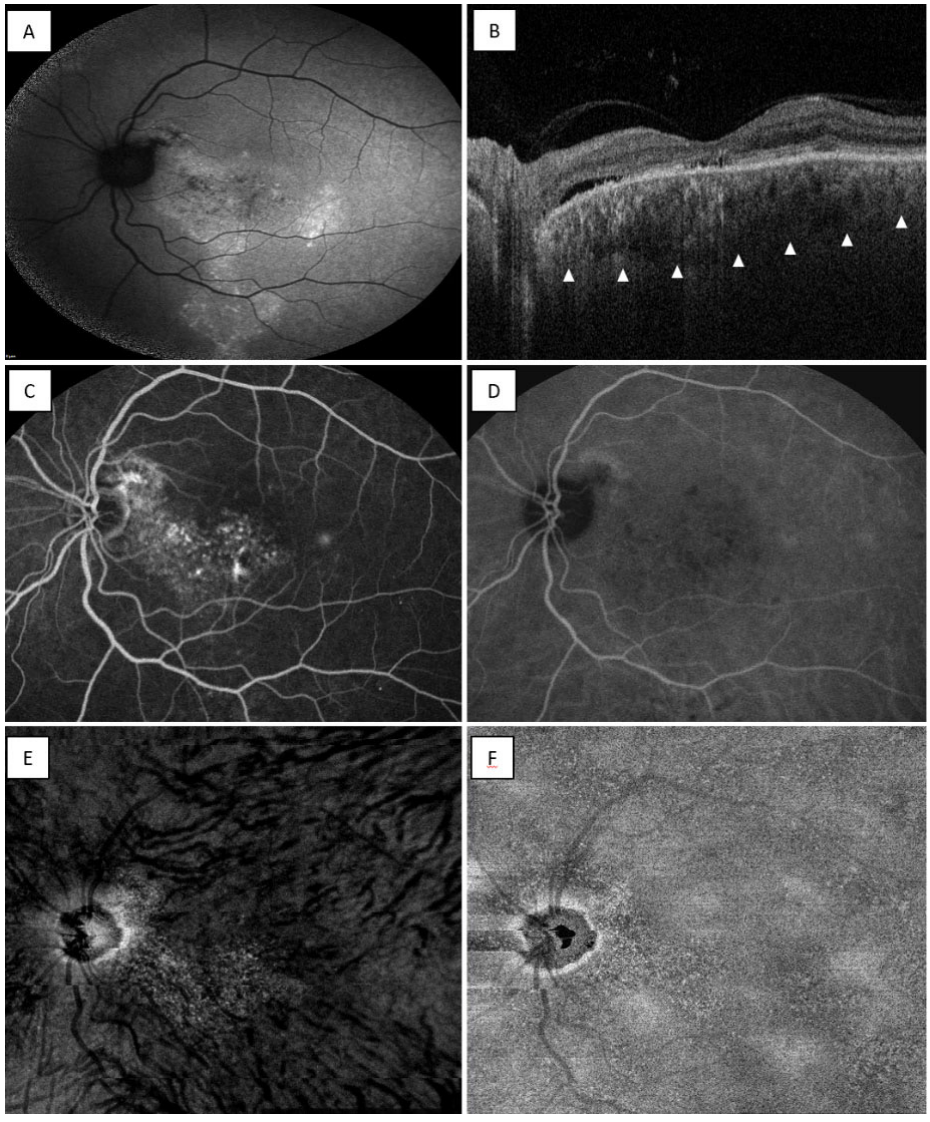

Figure 5. Multimodal imaging in peripapillary pachychoroid syndrome (PPS). A) Fundus autofluorescence in a 64-year-old man with PPS. Note the presence of hyper- and hypoautofluorescence in the peripapillary region and in the macula, in a typical pattern defined as "femur sign". B) Optical coherence tomography (OCT) scan through the fovea shows the presence of macular and peripapillary subretinal fluid. Note that the peripapillary choroid is thicker than the choroid in the temporal macula. C) Fluorescein angiography shows the presence of hyperfluorescent spots in the peripapillary region. D) Indocyanine green angiography demonstrates hyperpermeability in the peripapillary region and the macula. E) En-face OCT angiography shows the presence of dilated choroidal vessels in the peripapillary region. F) En-face OCT angiography at the level of the choriocapillaris shows the presence of flow alterations in the macula and in the peripapillary region

with choroidal hypertransmission and atrophy of the RPE, ellipsoid zone, and external limiting membrane.[53] Peripapillary pachyvessels are more noticeable in nasal than temporal regions. EDI-OCT detects intraretinal fluid with cysts in the nasal macula that extend to the temporal optic disc margin, accompanied by focal atrophy of the RPE, ellipsoid zone, and external limiting membrane in both eyes. This small cystoid space, otherwise known as a "peripapillary fluid pocket" has been thought to represent a possible entry of fluid from the choroid to the retina, and represents a biomarker of PPS.[53]

Peripheral Exudative Hemorrhagic Chorioretinopathy

PEHCR is a rare condition first described by Reese and Jones[54] in 1961, characterized by peripheral hematomas under the RPE. It has often been mistaken for choroidal melanoma, which requires different management approaches. At first, PEHCR was considered a peripheral variant of AMD due to shared clinical features such as hemorrhage and exudation, alongside macular drusen and RPE changes observed in some cases.[55] Recent research using EDI-OCT indicates that PEHCR may be a part of the spectrum of pachychoroid diseases.[56] Comparing choroidal vascular changes and thickness between PEHCR and healthy eyes, PEHCR eyes showed a gradual thickening of the choroid from the nasal to the temporal periphery. In contrast, healthy eyes exhibited maximum CT subfoveally. Moreover, choroidal vessel thickness tended to be greater in the PEHCR group compared to healthy eyes. These results indicate that the increased CT and pachyvessels in PEHCR support its classification as a pachychoroid disease.[56]

Subsequent findings on ICGA, such as abnormal choroidal vascular networks and polyp-like telangiectasis, suggested a potential link to PCV (Figure 3).[26,57] ICGA findings in PEHCR include polyps (0-59%), pathologic choroidal network (30-84%), and late hypercyanescence or leakage of uncertain etiology (60-62%).[57,58,59]

However, imaging PEHCR lesions with OCT can be challenging due to their peripheral location. Regardless, these lesions are often characterized by subretinal fluid or PEDs over Bruch's membrane without infiltration of the underlying choroid.[58–60] Additionally, OCT of the macula may show the spread of subretinal fluid, exudates, or the formation of macular fibrosis.

Indocyanine Green Angiography

ICGA enhances choroidal imaging due to the RPE's greater transparency to longer wavelengths. However, the main limitation remains its inability to localize features to specific tissue layers because of vertical summation.[61]

ICGA is a specialized imaging system that provides detailed visualization of the choroidal vasculature, contributing to our understanding of pachychoroid diseases. More recently, ultra-widefield ICGA has been introduced, significantly expanding our field of view, particularly in assessing peripheral choroidal features.[62,63] Ultra-widefield ICGA enables comprehensive *in vivo* visualization of the choroidal circulation, covering areas from the posterior pole to beyond the vortex vein ampullae.[64,65] This advanced imaging technique has been utilized to assess choroidal vascular changes in eyes affected by pachychoroid disease entities. The findings support the hypothesis that venous outflow congestion may contribute to the pathogenesis of these conditions.[66]

In CSC, ultra-widefield ICGA has identified several characteristic features, including dilation of choroidal veins,[67,68] choroidal venous anastomoses that do not adhere to the watershed zone between distinct vortex vein quadrants,[4,62] and asymmetric venous drainage causing enlarged or deflated vortex vein ampullae (Figure 1).[5,67,68] These changes are consistent with findings seen on EDI-OCT.[3]

A study using ultra-widefield ICGA imaging on 52 patients with various pachychoroid conditions determined that 88% of eyes exhibited choroidal venous anastomoses.[66,69] Furthermore, choroidal vascular hyperpermeability was noted in all eyes affected by pachychoroid-related conditions. Postoperative widefield ICGA identified vortex vein anastomoses in 10 out of 12 eyes within three months following vortex vein occlusions. These observations were accompanied by widespread ICGA hyperfluorescence in the quadrant where the occlusion had occurred.[66,69]

ICGA has always been the preferred method for diagnosing PCV. In the early phase of ICGA, one or more polyps may be visible. However, both flash digital fundus photography with ICGA and confocal scanning laser ophthalmoscopy systems have shown the ability to detect at least 80% of typical nodular lesions of PCV. Recent studies have proposed further classification of PCV subtypes based on appearances on ICGA and supported by choroidal vascular features observed on SD-OCT.[25]

On ICGA, pachyvessels are seen as clusters of relatively straight and dilated choroidal vessels. Other findings include dilation of choroidal veins, filling defects in the choroid, delayed arterial filling in the early phase, and focal or punctate hyperfluorescence in eyes with CSC, PCV, and FCE (Figures 1 and 3). These observations suggest the possibility of choroidal ischemia.[70,71,72] In the mid to late phase, ICGA reveals patchy areas of hyperfluorescence that correspond to the leakage and staining sites observed on fluorescein angiography. Previous studies have indicated that choroidal hyperpermeability is present in more than 90% of eyes with PPE and CSC[72] and 10-50% of those with PCV.[73,74]

Additionally, punctate hyperfluorescent spots were seen in the mid to late phases of ICGA in eyes affected by CSC and PCV.[74,75] Both diffuse and punctate hyperfluorescent spots appear in the contralateral eyes of CSC and PCV and persist even after the subretinal fluid has resolved. These observations suggest that choroidal alterations are likely the primary cause of these conditions.

Scleral Thickness Measurement

Alterations in scleral thickness may impact pachychoroid diseases such as CSC and can be examined through ultrasound biometry (UBM) and anterior segment (AS)-OCT. In CSC, compression of vortex veins can lead to choroidal venous

congestion, causing delays in choriocapillaris filling and ischemic areas, termed "venous overload choroidopathy".[76] However, the precise role of scleral changes, including thickness, in affecting vortex vein drainage and contributing to pachychoroid disorders remains uncertain.

Studies investigating anterior scleral thickness (AST) and subfoveal CT in CSC and PNV using SS-OCT and EDI-OCT found that patients with CSC/PNV had thicker AST compared to controls in addition to higher subfoveal CT. This suggests that a thicker anterior sclera may contribute to the speculated venous overload, triggering pachychoroid phenotypes.[76] Other studies also demonstrated thicker AST in hyperopic eyes and thinner AST in myopic eyes, consistent with previous findings. However, there was no notable difference in AST between sexes. Thickening of the anterior sclera might impede vortex vein outflow, potentially contributing to CT and the onset of pachychoroid disorders.[76]

One study primarily focused on AST in patients with CSC versus healthy individuals and aimed to evaluate the reliability of scleral thickness measurements obtained using UBM compared to AS-OCT. It was found that mean AST measured by AS-OCT was significantly higher in CSC cases compared to controls.[77] There was also a significant difference in AST measurements between AS-OCT and UBM in CSC cases, with AS-OCT yielding higher measurements. Although a positive correlation between AST measured by AS-OCT and UBM was observed, differences in scleral border demarcation and inclusion of episcleral tissue in AS-OCT images may have affected the measurements. Another limitation was that manual measurements with a digital caliper were considered more accurate in AS-OCT than in UBM. Therefore, it was concluded that AST measurements obtained by UBM did not align with those obtained by AS-OCT.[77]

Optical Coherence Tomography Angiography

The primary applications of OCTA are in research to understand etiopathogenesis, and in clinical settings to improve the diagnosis of pachychoroid neovascularization.

En-face OCT and OCTA scans can show choriocapillaris ischemia and choroidal anastomotic vessels, thereby improving the understanding of the pathophysiological mechanisms.[78] SS-OCT provides the benefit of longer wavelengths for greater tissue penetration along with the rapid capture of numerous images, greatly improving image quality. Moreover, the choriocapillaris structure can be visualized better in vivo by averaging en-face OCTA images. These show choriocapillaris ischemia/flow void areas corresponding to the location of dilated Haller vessels. The co-localization of dilated vessels, CT, and choriocapillaris attenuation has been demonstrated in cross-sectional OCT, with OCTA findings indicating reduced flow signal within the choriocapillaris.[79] It was suggested that the dilation of the large blood vessels in Haller's layer may compress the layers above it, including the medium-sized vessels in Sattler's layer and the choriocapillaris. This compression can disrupt blood flow in the choriocapillaris, leading to reduced oxygen supply in the overlying RPE and retina and promoting CNV.[45]

Chronic CSC is commonly associated with serous or flat, irregular PED. Before OCTA was used as a clinical tool to diagnose CNV, studies showed that 10% of eyes with CSC had CNV as a complication, and 33% of eyes with CSC had flat, irregular PED on macular OCT examination. PEDs were suggestive of type 1 CNV in 18% of the eyes with flat, irregular PEDs. The remaining 81% of these flat PEDs remained clinically quiescent under observation.[80] It was assumed that most flat PEDs were quiescent, undiagnosed CNV, or debris, pigment, or pachydrusen. The first studies using OCTA in CSC included only eyes with flat, irregular PED in order to assess the occurrence of CNV. In one study, in spite of the fact that dye angiography showed neovascularization in only 29% of the eyes, OCTA revealed type 1 neovascular tissue in 95% of the eyes.[81] In another study, ICGA revealed choroidal neovascular plaques in 42% of eyes (n=8), whereas OCTA showed CNV in 74% of eyes (n=14).[82] Overall, it was reported that OCTA was as good as fluorescein angiography as a gold standard technique for CNV, and even better than the combination of OCT, fluorescein angiography, and ICGA for the diagnosis of PNV (Figure 4). Demirel et al.[83] assessed the sensitivity and specificity of ICGA and OCTA and found that OCT was far more sensitive than ICGA (97.2% vs. 66.7%), while both techniques had 100% specificity. OCTA can non-invasively visualize neovascularization, shows vascular networks between the RPE and Bruch's membrane, is not affected by any kind of leakage, and may contribute to the diagnosis of CNV in suspicious cases. However, there are some shortcomings of dye angiography in chronic CSC. Diffuse RPE loss can cause widespread window defects and scattered points of RPE leakage in fluorescein angiography. Even ICGA, which is used to better visualize the problem, might show multiple patches of hyperfluorescence in the inner choroid that are also present with CNV. This can make things more complicated and hinder a correct diagnosis. In addition to those factors, the tendency of CNV to appear as a plaque in the late phase of angiography might not be the case in chronic CSC as is seen in AMD, which is characterized by a late-phase hypercyanescent plaque with a well-defined border.[84] Recently, Zola et al.[85] showed that leakage from type 1 CNV in central serous cases is less common in CSC than in AMD. Eyes with type 1 macular neovascularization in CSC are less likely to leak macromolecules from the macular neovascularization and accumulate them in the RPE and/or stroma, as evidenced by the late-phase hyperfluorescent plaque. In their series, Demirel et al.[83] reported that neovascularization showed hypercyanescence only in the early-mid ICGA phase in 10 of 24 eyes, but the border almost disappeared in the late phase of ICGA.

There might be some morphological distinctions between CNVs and pachychoroid, as there are many reports indicating differences in pathophysiology, genetic basis, and intraocular cytokine levels.[84] One study found that the indistinct pattern was more common in PNV eyes than in AMD eyes. However, the pruned vascular tree pattern, which is an OCTA sign of an inactive membrane, was less common in PNV eyes than in AMD

eyes with CNVs. Type 1 CNVs in PNV were characterized by a smaller CNV area and flow compared with type 1 CNVs in AMD.[86] Yanık et al.[86] used software that created a skeleton model from the Otsu binarization of en-face OCTA images and measured the total length and number of intersection points. Their study revealed differences not only in qualitative OCTA features but also in quantitative features. They reported that the macular neovascularization area was smaller, vessel density was lower, total vessel length was shorter, the number of intersection points was smaller, and fractal dimension showed less complexity in PNV compared to AMD. This form of CNV may represent an attempt at reforming the choriocapillaris, with a few anastomoses bringing sufficient oxygen and nutrients to the surrounding retina.[87]

Many studies found that SD-OCTA was not as good at diagnosing polypoidal vasculopathy as ICGA, but was better for visualizing the basal vascular network. A recent study suggested that SS-OCTA may be a better way to accurately detect both polypoidal lesions and branching vascular networks in PCV.[88] Bo et al.[89] found that polypoidal lesions are made up of dense or loosely mixed vascular structures at the edges of branching vascular networks or type 2 neovascularization. Polypoidal lesions are consistent with a neovascularization structure rather than an aneurysmal structure.

Discussion

The integration of advanced imaging techniques has considerably enhanced our understanding of pachychoroid spectrum diseases. Technologies like ICGA, OCTA, and EDI-OCT allow detailed visualization of the choroidal anatomy,[1,3,72,82,83] while UBM and AS-OCT visualize scleral anatomy, allowing the identification of key pathological features such as venous outflow congestion, choroidal vascular hyperpermeability, and anterior scleral thickening.[76,77] These findings suggest that scleral alterations play an important role in the development of pachychoroid diseases by impeding vortex vein outflow and contributing to CT.

Although these imaging advancements have undeniably provided critical insights into the pachychoroid spectrum of diseases, it is important to acknowledge the limitations and ongoing controversies within the field. For example, despite the high resolution and deep tissue penetration offered by OCTA and EDI-OCT, there remains variability in the interpretation of these images.[3,11,12,21] Differences in the diagnostic criteria and classification of pachychoroid diseases across studies suggest that further standardization is needed to ensure consistency and comparability of findings.

Additionally, there are controversies regarding the pathogenesis of pachychoroid diseases, particularly regarding the role of scleral changes and venous congestion in disease progression. While some studies suggest a direct link between anterior scleral thickening and choroidal congestion, others have not found consistent correlations, indicating that more robust longitudinal studies are needed to clarify these associations.[76,77] Looking ahead, future research should focus on longitudinal studies to establish causal relationships between scleral and choroidal changes and disease progression. Developing standardized imaging protocols and quantitative analysis methods will enhance the reproducibility and accuracy of these measurements.

The pathogenesis of the disease will be further clarified through development of imaging technologies, longitudinal studies that accurately track the disease stages, and investigations into genetic and molecular mechanisms underlying these structural changes. These steps will also help identify new targets for therapeutic intervention, which will improve patient care. At present, treatment options consist of anti-vascular endothelial growth factor agents for eyes complicated with CNV and/or polypoidal enlargement,[90,91] photodynamic therapy for the treatment of CSC,[92] and laser treatment such as subthreshold laser systems to enhance RPE function.[19]

Conclusion

In summary, advanced non-invasive imaging technologies with higher resolution and deeper penetration can lead to earlier detection of pachychoroid pathologies, more personalized treatment, and greater global accessibility to innovative diagnostics, ultimately improving patient care and outcomes.

Declarations

Authorship Contributions

Surgical and Medical Practices: S.D., A.Y., Concept: S.D., A.Y., J.C., Design: S.D., A.Y., N.V., J.C., Data Collection or Processing: S.D., A.Y., N.V., Analysis or Interpretation: S.D., A.Y., N.V., J.C., Literature Search: S.D., A.Y., Writing: S.D., A.Y., N.V., J.C.

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A Rare Intervention in a Rare Disease: Simultaneous Bilateral Keratoplasty in Bilateral *Acanthamoeba* Keratitis

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Abstract

The purpose of this report is to present simultaneous bilateral penetrating keratoplasty (PK) in *Acanthamoeba* keratitis (AK). A 42-year-old male with keratoconus, wearing bilateral hybrid contact lenses, presented with pain in the left eye. He had a history of intrastromal corneal ring segment placement in the right and PK in the left eye. His best corrected visual acuity (BCVA) was 20/640 in the right eye and 20/2000 in the left. Slit-lamp examination revealed a ring-shaped infiltration on the left. Despite two months of broad-spectrum topical antibiotic therapy, microbiological examination of corneal scraping samples was repeated but revealed no evidence of microbial agents. *In vivo* confocal microscopy findings were not compatible with AK. During the follow-up, corneal infiltration and stromal melt were observed in the right eye. Corneal scraping samples from the right eye were sent for microbiological examination, but again no microbial agents were identified. Histopathological examination revealed spherical cysts consistent with AK. Corneal perforation developed in the right eye, while simultaneous wound dehiscence occurred in the left eye. Since the patient had a history of renal failure, simultaneous bilateral tectonic-therapeutic PK was performed to minimize the risks arising from general anesthesia. Postoperative BCVA was 20/50 in the right eye and 20/125 in the left eye at 6 months. Diagnostic tools can be misleading in eyes with altered anatomy. Careful examination and a timely decision to perform tectonic-therapeutic PK are vital in preventing devastating complications.

Keywords: Bilateral *Acanthamoeba* keratitis, contact lens, simultaneous bilateral penetrating keratoplasty, tectonic and therapeutic keratoplasty

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Introduction

Acanthamoeba spp. are free-living protozoans found in contaminated water and soil.[1] Early diagnosis and treatment of *Acanthamoeba* keratitis (AK) is critical to prevent full-thickness corneal perforations, which in some cases are inevitable despite aggressive treatment.[2]

Herein, we aimed to report a patient who underwent simultaneous bilateral tectonic-therapeutic penetrating keratoplasty (PK) for bilateral AK. To the best of our knowledge, simultaneous bilateral PK, which is a rare practice, has not been previously reported in bilateral AK, which is also a rare disease.

Case Report

A 42-year-old male patient with bilateral keratoconus presented with redness, pain, photophobia, and decreased vision in the left eye for 2 months. He was referred to our clinic with a diagnosis of keratitis resistant to empirical therapy. At the referring clinic, microbiological analyses of corneal scraping samples, contact lenses, and the contact lens container were performed, and no microbial agents were reported. He received broad-spectrum topical antibiotic therapy and antiviral therapy. His medical history revealed that intrastromal corneal ring segments (ICRS) were implanted in the right eye 16 years ago and he had undergone PK surgery on his left eye 13 years ago. The patient also had a history of using hybrid contact lenses in both eyes. Best corrected visual acuity (BCVA) was 20/640 in the right and 20/2000 in the left eye. Slit-lamp examination revealed a clear cornea with ICRS in the right eye, and a ring-shaped corneal infiltration with deep stromal haze and surrounding corneal edema in the central cornea accompanied by a large corneal epithelial defect (Figure 1) in the left eye. Despite two months of broad-spectrum topical antibiotic therapy, microbiological examination of corneal scraping samples was repeated, but these investigations also revealed no evidence

of microbial agents. *In vivo* confocal microscopy (IVCM) was performed with the suspicion of AK. Although the typical cyst appearance could not be distinguished on IVCM, topical 0.02% chlorhexidine gluconate (4 times daily) was initiated due to the lack of response to prolonged antibiotic and antiviral therapies. Broad-spectrum topical antibiotic therapy (fortified vancomycin 50 mg/mL, ceftazidime 50 mg/mL, fluconazole 2 mg/mL) was continued simultaneously, as the possibility of a mixed infection could not be excluded. During follow-up, decreased vision in the right eye and severe pain were added to the clinical picture. On slit-lamp examination, superficial punctate infiltrates and stromal haze were observed in the central cornea. Corneal scraping samples from the right eye were sent for microbiological examination, and all yielded negative results. Biomicroscopic findings progressed rapidly and within days, an epithelial defect and mild stromal melting appeared (Figure 1) with constant severe pain in the right eye. IVCM was repeated for both eyes and showed rare round or ovoid hyperreflective cysts without a hyporeflective halo and severe loss of keratocytes. At the same time, the liberated stromal tissue in the stromal melt area was dissected from the right eye and sent for histopathological assessment. Histopathological examination revealed defective corneal epithelium, polymorphic inflammatory cells in an edematous stroma, neovascularization, and spherical cysts with the typical double ring sign consistent with AK (Figure 2). Topical 0.1% propamidine isethionate (Brolene®; Sanofi, UK), which does not have a commercial form in our country, was obtained and added to treatment. Within the first month of presentation, bilateral stromal melting developed despite comprehensive and intensive therapy. On day 41 of hospitalization, a full-thickness corneal perforation developed in the cornea corresponding to the ICRS, exposing the rings in the right eye. Simultaneous non-traumatic wound dehiscence occurred at the recipient-graft junction in the left eye. Therefore, emergency tectonic and therapeutic PK was planned for both eyes. Since the patient had a recent history of acute renal failure, simultaneous bilateral PK was performed in the same session to minimize the risks arising from general anesthesia. Donor corneal buttons for both eyes were obtained from the same donor, thus reducing the risk of graft rejection in the recipient eyes. Postoperative BCVA was 20/50 in the right eye and 20/125 in the left eye with clear grafts bilaterally and no recurrence during 6 months of follow-up (Figure 3).

Informed consent for all procedures and this report was obtained from the patient.

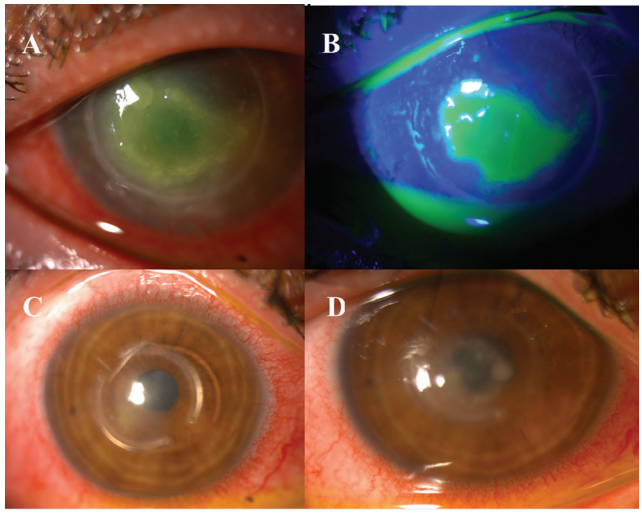

Figure 1. A, B) Anterior segment photographs of the left eye at presentation showing a large corneal epithelial defect in the central cornea with ring-shaped corneal infiltration and deep stromal haze. C, D) Anterior segment photographs of the right eye demonstrating the rapid progression of stromal invasion during follow-up

Discussion

Acanthamoeba, a free-living protozoan, can cause severe ocular morbidity and permanent blindness. Contact lens wear is a well-known risk factor for keratitis. Clinical manifestations of AK range from superficial punctuate keratopathy to full-

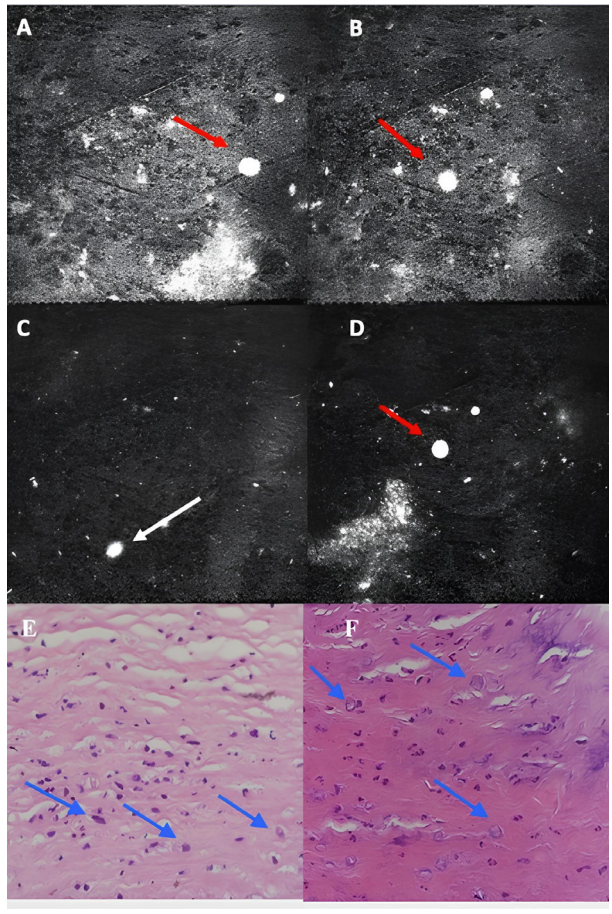

Figure 2. Representative *in vivo* confocal microscopy images of the patient's right eye (A, B) and left eye (C, D). Red arrows indicate round or ovoid hyperreflective cysts without a hyporeflective halo in the stroma. The white arrow indicates the amoeba form. E, F) Histopathological examination revealed defective corneal epithelium, polymorphic inflammatory cells in edematous stroma, neovascularization, and spherical cysts (blue arrows) with the typical double ring sign consistent with *Acanthamoeba* keratitis (hematoxylin and eosin x100, diastase-Periodic acid-Schiff x200)

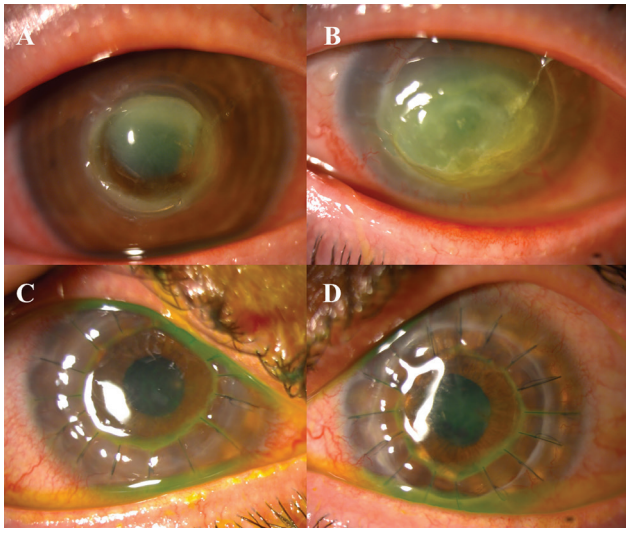

Figure 3. Preoperative anterior segment photographs of the right (A) and left (B) eye showing severe corneal melting and non-traumatic perforation. Ten weeks after simultaneous bilateral penetrating keratoplasty, anterior segment photographs showed clear grafts in both the right (C) and left (D) eye

thickness corneal perforations.[3,4] Although the importance of early diagnosis in AK is already emphasized, it involves number of challenges. In addition to manifesting with atypical findings, *Acanthamoeba* can mimic other keratitis agents.[5] This causes delay in treatment and may rarely lead to secondary complications.

Although involvement is usually unilateral, bilateral AK can also be seen in rare cases. The use of contact lenses stands out as a prominent risk factor in these cases.[6,7] Wilhelmus et al.[7] reported bilateral AK in 5 of 45 patients who used contact lenses bilaterally. Similarly, in the present case report, the patient had a history of using bilateral hybrid contact lenses.

A high index of suspicion is crucial for the timely diagnosis of AK, and early intervention improves outcomes. Treatment response and visual prognosis are excellent in the early stages, when signs such as superficial punctate keratopathy and subepithelial infiltrates predominate.[8] In our previous case report, we described Y-shaped linear epitheliopathy with negative fluorescent staining as an early sign of AK. With this early and exceptional finding of AK, that patient received timely treatment and had an excellent prognosis with a final BCVA of 20/20.[9] However, the prognosis is guarded in cases with deep stromal invasion and ring-shaped corneal infiltration. In its natural course, the infection quickly penetrates deeply into the stroma. Therefore, PK is almost always inevitable in advanced stages with progression to full-thickness corneal involvement.[8] Herein, the diagnosis of the patient was delayed, and therefore tectonic and therapeutic PK became imperative. The inconsistency between the diagnostic methods and the patient's clinical presentation is thought to play a major role in this situation.

The use of diagnostic tools is as important in the diagnosis of AK as the evaluation of clinical findings and risk factors. Microbiological evaluation of corneal scrape samples together with culture and polymerase chain reaction tests can identify *Acanthamoeba*.[2,8] Furthermore, IVCM is highly beneficial in demonstrating hyperreflective spherical cysts with the typical double ring sign, which is considered a specific finding of AK.[10] Occasionally, IVCM may fail to diagnose *Acanthamoeba*, as in this case report. Although IVCM was performed with the suspicion of AK at the time of admission, no compatible finding was detected. Rare cysts without a hyperreflective halo were seen when IVCM was repeated. However, histopathological examination confirmed cysts with double ring-sign, allowing the diagnosis of *Acanthamoeba* to be made. IVCM may have been misleading in this patient because of his history of ICRS in one eye and PK in the other eye. This highlights the limitation of IVCM in eyes where normal anatomy has been altered by anterior surface surgery. Therefore, it is important to act with a multidisciplinary approach when in doubt, to insist on investigations even if reliable diagnostic methods indicate otherwise, and to benefit from conventional methods such as direct light microscopy.

Another unique feature of this case of bilateral AK is that simultaneous bilateral PK was performed at the end of extended follow-up and interventions. Because of the already well-known perioperative and postoperative complications of PK, surgeons are often hesitant to perform bilateral surgery in the same session. However, the application of simultaneous bilateral PK for different indications has been reported in the literature, albeit rarely. Md Noh and Then[11] reported simultaneous bilateral PK due to spontaneous corneal perforation in a patient with Stevens-Johnson syndrome. Bhandari[12] described simultaneous bilateral PK in a patient with pseudophakic bullous keratopathy in one eye and corneal graft rejection in the other eye. In the present case, tectonic and therapeutic PK was performed in both eyes to preserve globe integrity. Since general anesthesia poses the risk of complicating preexisting acute renal failure, bilateral PK was performed in the same session instead of sequential surgery.

Despite the disadvantages and possible risks of simultaneous bilateral PK, it may be unavoidable and even favorable in certain situations. In addition to minimizing the risks associated with general anesthesia, as in the present case, the use of donor corneal buttons from the same donor may also minimize the potential immune response and consequently the risk of graft rejection in the recipient.[13] Tuft et al.[13] reported an interesting result in patients who underwent bilateral sequential PK. They showed that performing PK in the contralateral eye increased the risk of graft rejection in the eye that underwent PK first.[13] Thus, in the present case the donor corneal buttons were taken from the same donor, which seems to have been advantageous for this patient.

In conclusion, a high index of suspicion is crucial for early diagnosis and accurate management of AK. Although diagnostic tools such as IVCM are useful in AK, it can be misleading in eyes where normal anatomy has been altered by surgery. In these

cases, inconsistency between the results of diagnostic methods and the patient's clinical picture may delay the diagnosis and necessitate PK. To the best of our knowledge, this is the first report of simultaneous bilateral PK performed in bilateral AK, both of which are rare.

Ethics

Informed Consent: Obtained.

Declarations

Authorship Contributions

Surgical and Medical Practices: Ö.B.S., S.E., B.Y., C.Ş., Concept: İ.K., Ö.B.S., Design: Ö.B.S., Data Collection or Processing: N.F.E., C.Ş., S.E., Analysis or Interpretation: N.F.E., Ö.B.S., Literature Search: İ.K., Writing: İ.K.

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Case Report

Report of a Rare Syndromic Retinal Dystrophy: Asphyxiating Thoracic Dystrophy (Jeune Syndrome)

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Abstract

Jeune syndrome (JS), first described by Jeune as asphyxiating thoracic dystrophy, is an autosomal recessive osteochondrodysplasia with characteristic skeletal abnormalities and variable renal, hepatic, pancreatic, and ocular complications. Approximately 1 in every 100,000 to 130,000 babies is born with JS. Most patients with JS have respiratory distress due to inadequate lung development and many lose their lives due to respiratory failure. Those who survive have serious comorbidities. In terms of ophthalmological diseases, JS is classified among the hereditary syndromic retinopathies. Most, if not all, hereditary syndromic retinopathies can be analyzed in two main groups: inherited metabolic diseases and ciliopathies. The main cause of ocular pathologies in JS is genetic mutations in ciliary proteins that prevent normal function of retinal photoreceptor cells. Here we describe a patient with JS who presented with the complaint of night blindness. Although Snellen visual acuity was 20/20, the patient's visual function was severely impaired due to photoreceptor dysfunction caused by ciliopathy secondary to the genetic mutation. This case shows that in patients with syndromic comorbidities accompanying nyctalopia, even those with perfect visual acuity, hereditary retinal dystrophies should be considered and asphyxiating thoracic dystrophy (JS) included in the differential diagnosis. Multimodal retinal imaging, including structural and functional assessments, should be used for the diagnosis and genetic counselling should also be provided.

Keywords: Jeune syndrome, retinal dystrophies, nyctalopia, asphyxiating thoracic dystrophy, inherited retinal diseases

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Introduction

Jeune syndrome (JS), first described by Prasad and Prasad[1] as asphyxiating thoracic dystrophy, is an autosomal recessive osteochondrodysplasia with characteristic skeletal abnormalities and variable renal, hepatic, pancreatic, and ocular complications. Approximately 1 in every 100,000 to 130,000 infants is born with JS.[1]

Here we describe a patient with JS who presented with the complaint of night blindness.

Case Report

An 18-year-old boy with JS was referred to our retina clinic from the pediatrics clinic of our university. Detailed systemic and genetic examinations were performed. His parents are first cousins and he was born at term. His physical characteristics at presentation included a narrow rib cage, height of 110 cm, flattened nasal root, wide nasal tip, disproportionate shortening of all limbs (more pronounced the upper limbs), and short, thick fingers. He has no intellectual disability. In the exome sequencing panel performed on the Illumina Nextseq platform, homozygous variants were evaluated first due to the familial consanguinity. Then, OMIM genes associated with JS and primary ciliary dyskinesia were filtered. The results revealed a c21+26_21+33dupTGAGCGGG variation in the *TTC21B* gene that was homozygous in the patient and heterozygous in his parents. Ophthalmological examination revealed bilateral best corrected visual acuity of 0.9-1.0 decimal. Refractive errors were +1.00 diopter (D) spherical and +1.50 D cylindrical (95° axis) in the right eye and +1.25 D spherical and +1.50 D cylindrical (85° axis) in the left eye. Globe movements in all directions were normal bilaterally. Direct and indirect light reflexes were normal and there was no relative afferent pupillary defect bilaterally. No pathology was detected on bilateral slit-lamp examination. Central corneal thickness was

626 µm in the right eye and 642 µm in the left eye. Bilateral fundoscopic examination revealed retinal pigment epithelium (RPE) alterations. Changes in the RPE were observed both in the fundus examinations and in color fundus photographs taken with a Zeiss Visucam 500 fundus camera system (Figure 1). Fundus autofluorescence examination with the same system revealed a hyper-autofluorescent Robson-Holder ring (Figure 2). Optical coherence tomography (OCT) macula scan (Avanti RTVue XR) to evaluate the retinal architecture demonstrated fovea-sparing ellipsoid zone defects, thinning of the outer nuclear layer, and thinning of the reflex of the RPE-Bruch's membrane complex (Figure 3). Flash visual evoked potential test was performed in the electrophysiology clinic of our university. Amplitude and latency values were found to be within normal limits for both eyes. In the flash electroretinogram test, bilateral latency values were found to be within the normal range, while amplitude values were found to be severely low (Table 1). Other advanced tests could not be performed due to technical limitations in our electrophysiology laboratory. These results pointed to retinal dystrophy associated with ciliopathies caused by the *TTC21B* gene mutation.

Discussion

Asphyxiating thoracic dystrophy (JS) is a rare autosomal recessive ciliopathy characterized by multiple musculoskeletal abnormalities, multi-organ involvement, and variable severity. JS was first recognized in 1954.[2] One of the most commonly described defects is a mutation in the *DYNC2H1* gene.[3] The prevalence of JS is 1 in 100,000 to 130,000.[1] Children with JS often present with respiratory distress and recurrent infections in the neonatal period, although it has been found that respiratory problems tend to decrease with age in long-term survivors. Kidney, liver, and retinal function should be monitored regularly in these patients. Tüysüz et al.[4] stated that besides the clinical variability, prognosis also differs greatly among patients. It is difficult to differentiate JS from chondroectodermal dysplasia (Ellis-van Creveld syndrome).[5] There are also no genetic or biochemical markers that can be used effectively in the prenatal diagnosis of the disease.[6]

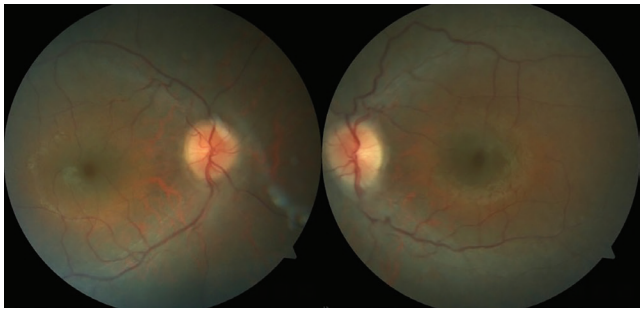

Figure 1. Color fundus photography revealed diffuse retinal pigment epithelial changes

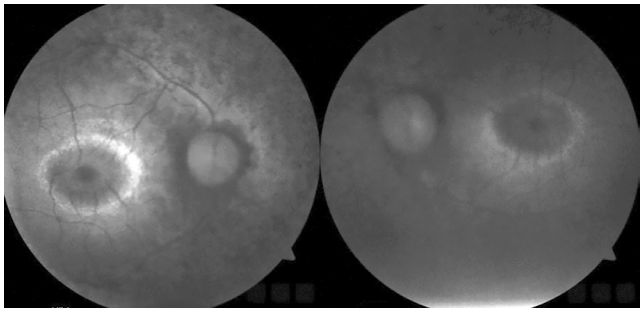

Figure 2. Fundus autofluorescence imaging revealed a hyper-autofluorescent Robson-Holder ring

Retinal dystrophies are a clinically and genetically heterogeneous group of degenerative diseases of the retina. Haim[7] described retinal dystrophies as a group of conditions with various clinical manifestations which are estimated to affect as many as 1 in 4,000 individuals. By more recent estimates, the prevalence is approximately 1 in 1,380, and 5.5 million people worldwide are believed to be affected.[8] Tatour and Ben-Yosef[9] reported that over 80 forms of syndromic inherited retinal diseases have been described and approximately 200 genes identified in association with these syndromes. They are classified into two major disease groups: inborn errors of metabolism and ciliopathies. Common manifestations include color blindness or night blindness, abnormalities of peripheral vision, and the subsequent progression to complete blindness in those with progressive disease. Many causative genetic defects have been identified.

The main cellular units responsible for visual phototransduction are rod and cone photoreceptors. Rhodopsin is composed of opsin protein and 11-cis retinal, a form of vitamin A. When light is absorbed by the retina, the structure of the opsin protein changes and the G-protein cascade begins.[10] Phototransduction is the process by which light signals are converted into action potentials in the retina, thus facilitating the perception of an image by the brain. During this process, photosensitive pigments are produced and recycled. Retinal dystrophies result from both photoreceptor abnormalities

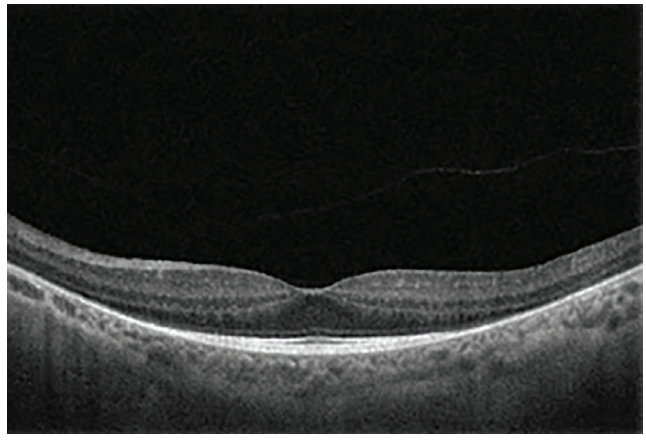

Figure 3. Optical coherence tomography macula section demonstrated fovea-sparing defects of the ellipsoid zone, thinning of the outer nuclear layer, and thinning of the reflex of the RPE-Bruch's membrane complex

RPE: Retinal pigment epithelium

Table 1. Flash visual evoked potential (VEP) and electroretinography (ERG) results interpreted according to International Society for Clinical Electrophysiology of Vision criteria (normal values for VEP: N2 latency <90 ms, P2 latency <120 ms, amplitude: >3.5 mV; for ERG: a wave latency <55 ms, b wave latency <85 ms, amplitude >10 mV). The a-wave represents photoreceptor response, while the b-wave represents activities of bipolar cells or Müller cells

Flash VEP	**N2**	**P2**	**Amplitude**	
	Latency	**Latency**		
Bilateral	Normal	Normal	Normal	
Right	Normal	Normal	Normal	
Left	Normal	Normal	Very low	
Flash ERG	**a**	**b**	**Amplitude**	**b/a**
	Latency	**Latency**		
Right	Normal	Normal	Very low	a wave dominant
Left	Normal	Normal	Very low	a wave dominant

and phototransduction defects. Genetic tests can be used to analyze the mutations involved. Management aims at slowing the degenerative process, treating complications, and helping patients to cope with the social and psychological impact of blindness.[11]

Nyctalopia, or night blindness, is a condition that makes it difficult or impossible to see in relatively dim light. It is a symptom of many eye diseases. Night blindness can be present from birth or result from injury or poor nutrition. It can be described as inadequate adaptation to darkness. The most common cause of nyctalopia is retinitis pigmentosa, a disorder in which the rod cells in the retina gradually lose their ability to respond to light.

Multimodal structural and functional imaging modalities such as spectral-domain OCT, color fundus photography, fundus autofluorescence, and electrophysiological testing are used in the diagnosis and follow-up of retinal dystrophies. The Robson-Holder ring is among the retinal examination findings and consists of perifoveal hyper-autofluorescence surrounding centrally preserved retinal structure and function. Early descriptions attributed Robson-Holder rings to increased RPE lipofuscin and photoreceptor pigment changes. However, due to an unmasking effect, reduced macular pigment overlying the RPE increases the intrinsic fundus autofluorescence. It is likely that one of the mechanisms responsible for the hyperautofluorescent rings is reduced macular pigment at greater eccentricities from the foveal center.[12]

In our case, we reported a patient with Snellen best corrected visual acuity of 20/20 but night blindness. Genetic testing revealed a mutation in the *TTC21B* gene compatible with JS. The patient also had musculoskeletal changes phenotypically consistent with the disease. Although visual acuity was 20/20, the patient had difficulty in night vision. Multimodal retinal imaging showed changes compatible with retinal dystrophy. OCT showed a preserved fovea but outer retinal zone atrophy. Color fundus photography and fundus autofluorescence imaging indicated a preserved macula and peripheral chorioretinal atrophy. Electrophysiological test results were also consistent with retinal dystrophy.

As in our case, mutations in the *TTC21B* gene cause ciliopathies in humans. Specialized sensory cilia in the photoreceptors of the eye are responsible for converting light stimuli into neural responses. Inherited retinal degenerations are caused by mutations in several photoreceptor-specific and common ciliary genes.

Although our patient had 20/20 visual acuity according to Snellen chart, his visual function was severely impaired due to photoreceptor dysfunction caused by ciliopathy secondary to the genetic mutation.

In conclusion, asphyxiating thoracic dystrophy (JS) should be kept in mind during the differential diagnosis of retinal dystrophies that cause nyctalopia, and multimodal retinal imaging, including structural and functional assessments, should be used for diagnosis.

Ethics

Informed Consent: Obtained.

Declarations

Authorship Contributions

Surgical and Medical Practices: G.T., B.A., Concept: G.T., B.A., Design: G.T., B.A., Data Collection or Processing: G.T., B.A., Analysis or Interpretation: G.T., B.A., Literature Search: G.T., B.A., Writing: G.T., B.A.

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

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A Sandwich-Type Double-Layer Amniotic Membrane Graft for Repairing Myopic Macular Hole-Related Retinal Detachment in a Child with Knobloch Syndrome

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Abstract

This case report describes a surgical technique using double-layer human amniotic membrane (hAM) grafting to repair a high myopic macular hole (MH)-related chronic retinal detachment (RD) with subretinal bands in a child with Knobloch syndrome. A 4-year-old boy diagnosed with Knobloch syndrome presented with macular atrophy in the right eye and chronic total RD with subretinal bands associated with a myopic MH in the left eye. The surgery involved an encircling band, pars plana vitrectomy, and subretinal band extraction through a retinotomy. The retinotomy and MH were sealed using hAM with a 5000 centistoke (cS) silicone oil (SO) tamponade. RD recurred two weeks postoperatively due to hAM contracture, leading to MH reopening. A second intervention included replacing the contracted graft with two larger hAM grafts; the first positioned under the MH and the second over the MH in a sandwich configuration, with 5000 cS SO tamponade. Eighteen months after SO removal, a flat retina, closed MH, and ambulatory vision were achieved. In conclusion, double-layer hAM grafting provides a strong seal for MH in high myopia-associated RD where conventional techniques fail.

Keywords: Pediatric retinal detachment, human amniotic membrane, Knobloch syndrome, macular hole-related retinal detachment, pediatric high myopia

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Introduction

Knobloch syndrome, first described in 1971,[1] is a rare genetic disorder caused by mutations in the *COL18A1* gene and characterized by extreme myopia, vitreoretinal degeneration, retinal detachment (RD), and occipital encephalocele.[2] Traditionally, RD in Knobloch syndrome has been attributed to peripheral breaks rather than macular holes (MH).[1] However, recent studies have revealed that RD may occur secondary to full-thickness MH, with standard treatment procedures demonstrating low success rates in these cases.[3]

Herein, we describe a genetically confirmed case of Knobloch syndrome in a 4-year-old patient who underwent vitreoretinal surgery using a double-layer human amniotic membrane (hAM) grafting technique to address recurrent MH-related RD. We discuss the surgical challenges associated with Knobloch syndrome and the potential benefits of this innovative approach in complex cases.

Case Report

A 4-year-old boy with infantile myopia, born full-term without complications, was referred for RD in his left eye. His parents reported first-degree consanguinity but no known familial history of retinal disease. The patient had no siblings. The diagnosis of Knobloch syndrome was confirmed by identifying *COL18A1* mutations.

Visual acuity was counting fingers at 0.5 meters for the right eye and at 1 meter for the left eye. Retinoscopy revealed refractive errors of -5.50 diopters (D) in the right eye and -6.00 D in the left eye. Intraocular pressure was normal and anterior segment examination was unremarkable in both eyes. Fundus examination revealed pigmentary retinopathy and macular atrophy in the right eye, while there was chronic total RD with subretinal bands associated with MH in the left eye (Figure 1).

The surgery involved an encircling buckle combined with pars plana vitrectomy. Inducing posterior hyaloid detachment was highly challenging due to unusually strong vitreomacular adherence and required bimanual maneuvers. As the tight subretinal bands were preventing attachment of the retina, we performed a small retinotomy at the most robust portion of the bands, located inferonasally near the optic nerve head, to cut and remove as much of the bands as possible. Staining and peeling of the internal limiting membrane (ILM) could not be performed despite multiple attempts. Therefore, a hAM graft was utilized. Both the retinotomy and the MH were sealed by placing a piece of hAM into the holes (under the retina) with the aid of perfluorocarbon liquid (PFCL). This was followed by fluid-air-silicone oil (SO) 5000 centistoke exchange. No laser was applied to the retinotomy (Video 1).

The retina was flat on the first postoperative day. However, recurrent RD with re-opening of the MH occurred by the second postoperative week due to graft contracture (Figure 1F).

Subsequently, a second intervention was performed under general anesthesia. The retinotomy site was well-sealed with graft in place. The graft was also in place at the macula, adhering to the retinal pigment epithelium (RPE), but had contracted. This created a space for fluid leakage that led to MH reopening and RD recurrence. A fluid-air exchange was performed to flatten the retina under air and PFCL was used to keep it in place. Two separate amniotic grafts, both larger than the MH size, were prepared. The first graft was implanted under the neurosensory retina to cover the floor of the hole, with the chorionic side facing the RPE. The second graft was placed over the surface of the retina (epimacular) with the chorionic side facing downward, creating a sandwich-like covering under and over the MH. Care was taken during the removal of the PFCL to avoid displacement of the grafts, particularly the epimacular graft. The PFCL was aspirated cautiously with a low-vacuum mode from around the margins of the heavy liquid. Upon confirmation of dryness and stability of the grafts, SO was injected, concluding the surgical procedure (Video 1). The SO was removed at postoperative 3 months. The retina remained attached, and the MH stayed closed during the 18-month follow-up period (Figure 2).

Discussion

Pars plana vitrectomy in pediatric and inherited retinal diseases differs significantly from that in the general population, both in the procedure itself and the unique challenges it presents. Vitreoretinal surgeons face additional difficulties during surgical steps such as posterior hyaloid separation, and the chronic nature of RD in pediatric cases further complicates the procedure.[1] Vitreoretinal adhesion is even stronger in Knobloch syndrome, often making posterior hyaloid detachment nearly impossible without inducing new retinal breaks, thereby making the surgery very challenging. Additionally, ILM peeling is always an issue in high myopic eyes. Since the ILM is underdeveloped in young children, routine MH repair techniques are often insufficient, requiring additional measures such as the use of

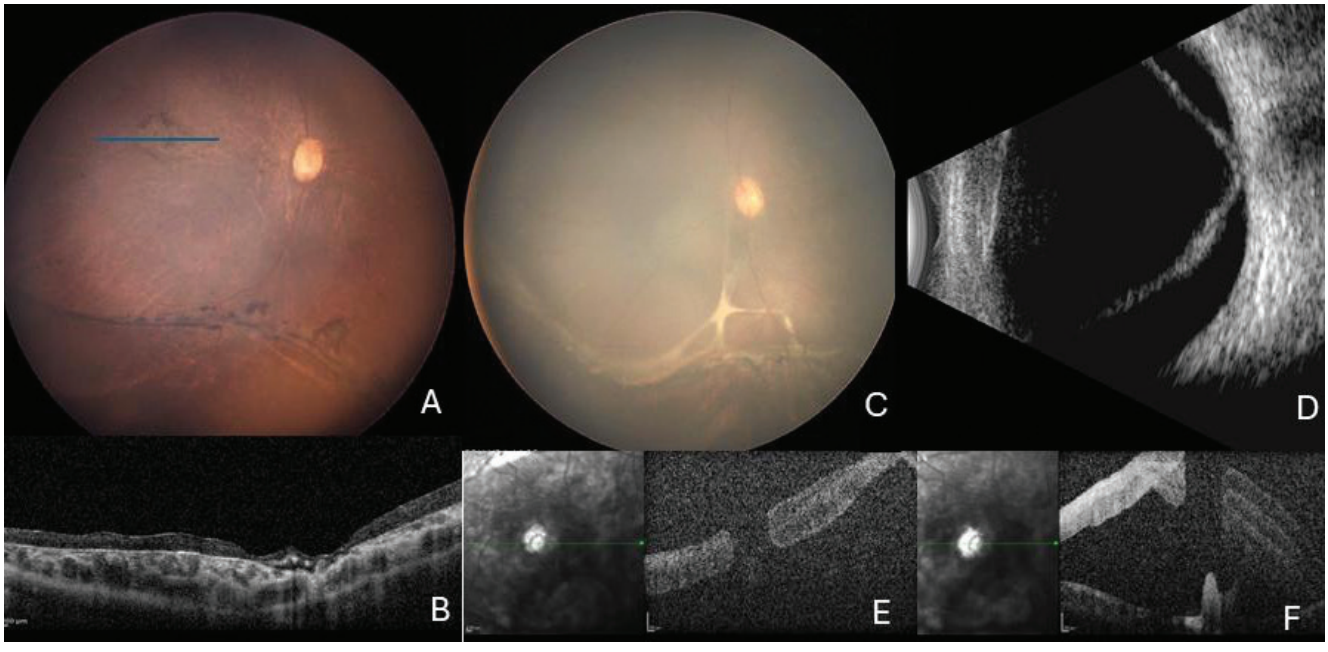

Figure 1. A) Colored fundus image of the right eye showing retinal pigmentary changes and central atrophy. B) Central optical coherence tomography (OCT) of the right eye showing the macular atrophy (cross-section from blue line in panel A). C) Fundus image of the left eye showing macula-off retinal detachment (RD) and inferiorly located thick subretinal bands. D) B-scan of the left eye revealing V-shaped total RD. E) OCT demonstrating macula-off RD with full-thickness macular hole in the left eye. F) Reopened macular hole 2 weeks after surgery in the left eye

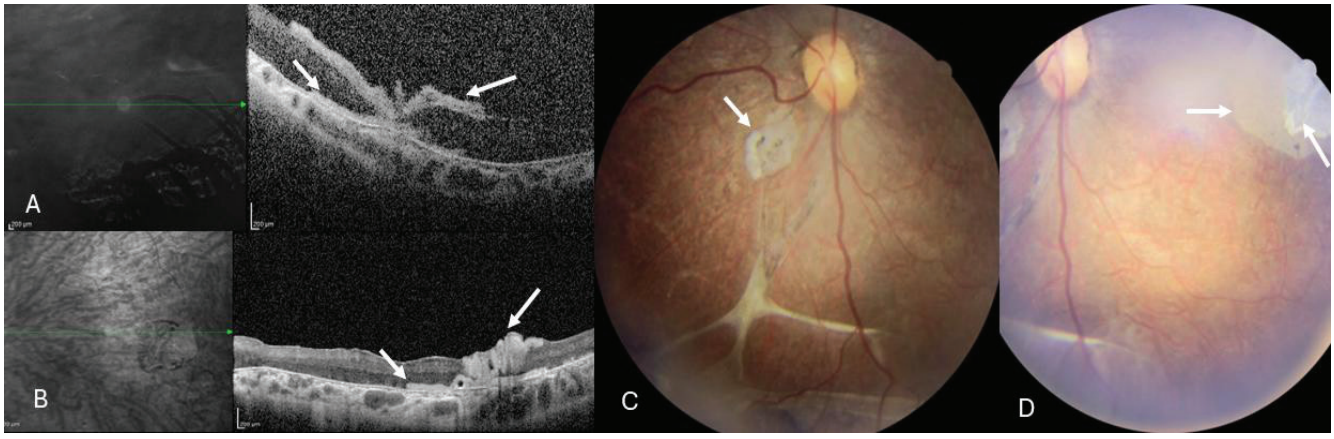

Figure 2. Optical coherence tomography images obtained 3 months (A) and 12 months (B) after the second surgery revealing attached retina with closure of the full-thickness macular hole sealed with inner and outer human amniotic membrane (hAM) grafts (arrows). C) Colored fundus image showing the retina is attached and the retinotomy is well-sealed with the hAM graft (arrow). Also note the residual subretinal bands inferiorly. D) Partial image of the macula (due to poor cooperation of the child) showing the closure of the full-thickness macular hole with 2 hAM grafts, one under and one over the macula (arrows)

a sealing material like hAM grafts. These grafts have been utilized successfully to treat challenging and recurrent RD cases associated with high myopic MH, yielding satisfactory visual and structural outcomes.[4] They are proposed to stimulate the regeneration of the exterior retinal layers, including the external limiting membrane and the ellipsoid zone, facilitating hole closure and leading to favorable visual and anatomical outcomes.[5] However, hAM grafts may migrate or contract, leading to failure of the surgery. A sub-neurosensory graft larger than the MH increases the likelihood of closure, but placing a larger graft under the retina requires more complex maneuvers and may risk damaging the RPE. Additionally, placing the graft with the chorionic surface facing the RPE is very important to achieve good adhesion, but it is not always easy to discriminate the correct side of the graft. In our experience, the risk of contraction is much higher when the graft is not placed in the proper orientation. If the graft is placed over the retina, then the risk of migration during or after the operation increases even more.

In the presented case, the first hAM graft probably contracted due to incorrect graft orientation. As a result, the graft could not seal the MH, leading to recurrent RD. During the second operation, a new technique of sandwich-like double layer grafting was attempted. A large hAM graft was placed under the MH, with another graft positioned over the hole, sandwiching the edges of the hole between the two layers. The hAM acts as a scaffold for tissue regeneration, potentially facilitating both MH repair and reattachment of the retina. The anti-inflammatory and anti-scarring properties of the membrane may also assist in reducing postoperative complications. Some studies have recommended subretinal placement of hAM with an aim to promote RPE regrowth,[6] while others suggest that epimacular grafts may offer better outcomes.[7] The combined use of both grafts may stimulate a dual process which could assist stronger healing. However, a potential disadvantage might be slightly impaired macular function due to the double-layered graft. Therefore, this double-layer sandwich technique may be reserved for challenging MH cases associated with high myopia and RD. To the best of our knowledge, this is the first case in the literature treated with this technique.

Ethics

Informed Consent: Obtained.

Declarations

Authorship Contributions

Surgical and Medical Practices: Ş.Ö., E.Ö.Z., Concept: O.O.A., Ş.Ö., E.Ö.Z., Design: E.Ö.Z., Ş.Ö., Data Collection or Processing: O.O.A., E.Ö.Z., Analysis or Interpretation: O.O.A., Literature Search: O.O.A., Writing: O.O.A., E.Ö.Z., Ş.Ö.

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

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Video 1. Displaying the details of both operations and the outcomes sequentially

https://www.youtube.com/watch?v=UkaPaXKlF8U&feature=youtu.be