ISSN: 2008-2010; eISSN: 2008-322X

JAN 2023
VOLUME 18
NUMBER 2

JOURNAL OF OPHTHALMIC & VISION RESEARCH

Official Publication of the Ophthalmic Research Center
Affiliated to Shahid Beheshti University of Medical Sciences

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Print ISSN 2008-2010;
E-ISSN 2008-322X

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E-ISSN 2008-322X

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The Journal of Ophthalmic and Vision Research is a peer-reviewed, open-access journal published quarterly on behalf of the Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences with the mission to disseminate information, viewpoints and questions about eye diseases, research, clinical and laboratory science, and education. The journal aims to advance the science, technology, ethics and art of ophthalmology through research and education worldwide. The scope of the journal is intended to include not only clinical ophthalmology, but related disciplines in basic sciences that contribute to the knowledge and science of vision.

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E-mail: labbafi@gmail.com & jovrjournal@gmail.com
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Published by

Knowledge E Office 4401–02 ,4404
Jumeirah Bay X2 Tower
Jumeirah Lakes Towers (JLT)
P.O. Box 488239
Dubai, UAE
Website: www.knowledgee.com

Print ISSN 2008-2010;
E-ISSN 2008-322X

JOURNAL OF
OPHTHALMIC AND VISION RESEARCH

Official Publication of the Ophthalmic Research Center

VOLUME 18, ISSUE 1, JANUARY 2023

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Editorial

Surgically Managed Orbital Tumors: A Case Series from a Referral Center in Iran

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J Ophthalmic Vis Res 2023; 18 (2): 141–142

The spectrum of orbital tumors is wide, including a variety of benign and malignant neoplasms. The reported incidence of different orbital tumors depends on several variables related to the geographic location of the study center and many other factors related to the type of study performed.

The effect of geographic location is well illustrated by the reported incidence of orbital retinoblastoma. For example, in a study on pediatric orbital tumors from Turkey, secondary orbital retinoblastoma accounted for 33% of cases, a rate much higher than that reported from more economically developed countries.[1]

The selection criteria of the study affect the reported incidence of orbital tumors in many ways. Whereas some studies include all clinically, radiographically, and pathologically diagnosed orbital space occupying tumors and pseudotumors,[2] others report only pathologically proven cases.[3]

The age distribution of the included patients will have significant effects on the results of the study as the types of orbital tumors seen in children are drastically different from those reported in adults. In studies reported from the United States on orbital tumors in children the most common tumors are benign cystic and vascular lesions but lymphoproliferative lesions are the most common tumors reported in older adults.[4–6]

The characteristics of the reporting facility where the study was performed can also impact the results of the study. In a study from a large ocular oncology center, of the secondary orbital tumors, 29% were orbital extension of uveal melanoma and 13% were orbital extension of conjunctival melanoma.[2] Majority of these patients were referred for treatment of the primary uveal or conjunctival melanoma and were found on further investigation to have orbital involvement. Similarly, in another study from a comprehensive cancer center in the United States, the most common orbital tumors were found to be secondary tumors (26% of cases).[7]

In this issue of the *Journal of Ophthalmic and Vision Research*, Bagheri and coworkers report the results of a retrospective study on space-occupying lesions of the orbit from a referral ophthalmology center in Tehran, Iran.[8] Their study includes orbital tumors that were managed over a 12-year period between 2008 and 2020 and had a definite histopathological diagnosis.

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Received: 31-08-2022 Accepted: 10-11-2022

Access this article online

Website: https://knepublishing.com/index.php/JOVR

DOI: 10.18502/jovr.v18i2.13178

How to cite this article: Mashayekhi A. Surgically Managed Orbital Tumors: A Case Series from a Referral Center in Iran. J Ophthalmic Vis Res 2023;18:141–142.

The requirement for a histopathological diagnosis is both a strength and a limitation of this study. On the one hand, diagnosis of orbital space-occupying lesions based on histopathological evaluation is more accurate than that based on clinical and radiological studies alone. On the other hand, this requirement leads to exclusion of many orbital space-occupying lesions that do not undergo surgical resection. For instance, a small orbital tumor with radiological features consistent with a cavernous hemangioma incidentally discovered in an asymptomatic patient is more likely to be observed and therefore would not have been included in the study. In the study by Shields and coworkers, only half of the presumed cavernous hemangiomas of the orbit underwent surgical removal.[2]

The study by Bagheri and coworkers includes patients of all ages, from 1 to 94 years, but is more skewed toward younger patients with a mean age of 31 years and with only 12% of the patients older than 60 years. It is therefore no surprise that dermoid cysts are the most common tumors in this study (one-third of all cases) and orbital lymphoma comprises only 4% of all the orbital tumors. In comparison, in the study by Shields and coworkers, only 6% of the tumors were cystic and 10% were lymphoid or leukemic.[2]

The geographic location of the medical center in which the patients were treated by Dr Bagheri and his coworkers, the capital city of Tehran, could have affected the results of their study. Although as a tertiary referral medical facility, the Labbafinejad Medical Center provides medical care to patients from different parts of the country, it is quite likely that most of their patients were from Tehran or surrounding areas where there is easier access to high-quality medical care.

A noteworthy finding of the study by Bagheri and coworkers is the absence of any cases of orbital invasion by retinoblastoma. Although I am not aware of any older studies from Iran, in an older study from Turkey including patients seen between 1963 and 1993, about one-third of pediatric orbital tumors were secondary orbital invasion by retinoblastoma.[1] Similarly, in a study that included patients managed in Saudi Arabia in the 1980s, 32% of pediatric orbital tumors proved to be orbital invasion of retinoblastoma.[9] A more recent study from a tertiary eye center in Saudi Arabia including pediatric patients managed between 2000 and 2013 does not show any cases of orbital retinoblastoma.[10] The absence of orbital invasion by retinoblastoma in the studies by Bagheri and coworkers and by Alkatan and coworkers most likely are due to improved medical care in the areas served by the respective treating medical facilities allowing timely diagnosis and treatment of retinoblastoma.

The study by Dr Bagheri and his colleagues provides important information on the distribution of surgically resected orbital tumors in Iran and the authors should be commended for their efforts. Further studies on this subject from medical centers in other parts of the country are necessary to provide a more comprehensive view of the distribution of orbital tumors in the country.

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Original Article

Surgical Punctal Occlusion; Combined Lacrimal Canaliculi Cauterization and Punctal Suturing for Severe Dry Eye

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Abstract

Purpose: To evaluate the treatment outcome of surgical punctal occlusion with combined canaliculi ablation and punctal suturing in patients with severe dry eye.

Methods: Eleven eyes of seven patients were diagnosed with severe dry eye with decreased lacrimal secretion and were refractory to treatment with various eye drops and/or had repeatedly experienced loss of punctal plugs, and continued to experience subjective symptoms received surgical punctal occlusion. In 20 puncta, lacrimal canaliculi ablation was performed along the entire length of the lacrimal canaliculus where a diathermy needle could be inserted. After resection of the annulus fibrosus in the peri-punctal area, tight cross-stitch suturing of the puncta was performed with 8-0 absorbent thread. Visual acuity, corneal staining score according to the area (A) and density (D) classification, and Schirmer tear test (STT); tear break up time (tBUT); and subjective symptoms assessed by the University of North Carolina (UNC) and Dry Eye Management Scale were compared before and one year after surgery.

Results: Recanalization occurred in 1/20 puncta (5.0% at month 5) in 1/11 eyes. Student's *t*-test showed significant improvement at one year compared with preoperative values for LogMAR value ($P = 0.019$), corneal staining score A ($P = 0.00003$) and D ($P = 0.0003$), STT ($P = 0.004$), and subjective symptoms ($P = 0.015$). No change was shown in tBUT and no serious adverse event occurred.

Conclusion: This improved, minimally invasive surgical procedure has a low recanalization rate and achieves both objective and subjective improvements at one year.

Keywords: Cauterization; Dry Eye; Lacrimal Canaliculi; Lacrimal Puncta; Punctal Occlusion

J Ophthalmic Vis Res 2023; 18 (2): 143–149

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Received: 31-08-2022 Accepted: 10-11-2022

Access this article online

Website: https://knepublishing.com/index.php/JOVR

DOI: 10.18502/jovr.v18i2.13179

How to cite this article: Kuroda K, Toshida H, Sorita Y, Ichikawa K, Matsuzaki Y, Ohta T. Surgical Punctal Occlusion; Combined Lacrimal Canaliculi Cauterization and Punctal Suturing for Severe Dry Eye. J Ophthalmic Vis Res 2023;18:143–149.

INTRODUCTION

Dry eye disease is known not only to cause discomfort but also to be associated with keratoconjunctival epithelial injury and decreased visual acuity.[1–4] Dry eye symptoms include dryness, redness, foreign body sensation, heavy sensation, pain, light sensitivity, discharge, itching, and eye fatigue with varying severity. An increasing number of treatment options are available for dry eye, including various types of eye drops and procedures for punctal closure.[5] In particular, punctal plug insertion is the first choice for punctal closure because it is a simple, minimally invasive procedure.[5–8]

Secondary Sjogren's syndrome associated with collagen diseases such as rheumatism, cicatricial pemphigoid, and chronic Stevens–Johnson syndrome decreases lacrimal secretion, which causes dry eye.[4, 5] In patients with severe dry eye, subjective symptoms include eye discomfort and eye pain and keratoconjunctival epithelial impairment. Many patients are refractory to treatment, for example, they show no improvement with eye drops and repeatedly lose punctal plugs; furthermore, insertion of a punctal plug often is difficult, and granulation may form after insertion of a punctal plug.[9] In such severe cases, surgical punctal closure is indicated, for example, by lacrimal canaliculi ablation.[10–23]

We evaluated the postoperative outcome of the surgical punctal occlusion with combined lacrimal canaliculi cauterization and punctal suturing for severe dry eye, which was a minimally invasive procedure, obtained relatively good results that were maintained even one year after surgery.

METHODS

Patients

We recruited consecutive patients who visited the Department of Ophthalmology at Juntendo University Shizuoka Hospital, Shizuoka, Japan, from June 2018 through March 2021, and had a diagnosis of severe dry eye with decreased lacrimal secretion, were refractory to treatment with various eye drops, and had repeatedly experienced loss of punctal plugs. Participants were patients with a definitive diagnosis of dry eye according to the Asia Dry Eye Society diagnostic criteria,[2] which include having at least one subjective symptom and a tear break-up time (tBUT) of 5s or less. The criteria for surgical intervention were being refractory to treatment with various eye drops for dry eye; loss of punctal plugs after repeated insertion; persistent subjective symptoms, such as eye pain and sense of a foreign body; and severe dry eye with decreased lacrimal secretion associated with keratoconjunctival impairment. Eleven eyes in seven patients who were followed-up for more than one year after punctal closure were included in the study.

Procedures

The study protocol was reviewed and approved by the ethics committee of Juntendo University Shizuoka Hospital, Japan, and the approval number is 809 (approved 12.02.2021). All patients signed the informed consent form to participate in the study. Patients provided written informed consent, and the study was performed in strict adherence with the guidelines for human studies and the World Medical Association Declaration of Helsinki. First, for local anesthesia, 1% xylocaine containing epinephrine was subcutaneously injected at the peri-punctal area and directly into the punctum [Figure 1A]. A 25-gauge diathermy needle with a diameter of 0.51 mm was inserted into the canaliculi about 2 mm vertically from the punctum [Figure 1B], and similar to the insertion of the nasolacrimal bougie, the tip of the diathermy needle was directed horizontally and inserted through the canaliculi to the place where it appeared to have reached the lacrimal sac. Next, the entire length of the canaliculi epithelium (about 8–10 mm) was cauterized while the inserted diathermy needle was slowly removed. To prevent recanalization of the canaliculi and facilitate closure of the punctum by suturing, the ring-shaped annulus fibrosus around the lacrimal punctum was incised parallel to the eyelid margin with a micro-scissor [Figure 1C]. Then, the incised skin around the punctum was cauterized with a diathermy needle in the same manner as for hemostasis, and a diathermy needle was inserted to cauterize the inside and outside of the punctum again. In the final step, the punctum was sutured with cross-stitches of 8-0 Vicryl absorbent thread across the punctum [Figures 1D & 1E], and the operation was completed [Figure 1F]. After the operation, 1.5% levofloxacin hydrate ophthalmic

Table 1. Background and subjective symptoms of the patients.

Case	Age (yr)	Gender	Background or diseases	Side	Upper/Lower	Follow-up months	LogMAR	
							Pre	Post
1	70	Male	Depression	Right	U + L	12.1	0.097	0.000
2	38	Female	Microphthalmos	Left	U + L	14.4	1.000	0.824
3	55	Female	RA, SS	Right	U + L	12.1	0.000	–0.079
				Left	U + L	12.1	–0.079	–0.079
4	71	Male	RA	Right	U + L	14.5	1.000	0.523
				Left	U + L	14.5	0.523	0.301
5	36	Male	SJS, schizophrenia	Right	L	12.7	0.155	0.000
				Left	L	12.7	0.523	0.523
6	46	Female	SS	Right	U + L*	12.7*	–0.079	–0.176
				Left	U + L	12.7	–0.079	–0.176
7	81	Female	SS	Left	U + L	11.6	0.523	0.000
Mean ± SD	52.7 ± 15.4					12.3 ± 2.4	0.326 ± 0.413	0.151 ± 0.338
P-value							0.019	

RA, rheumatoid arthritis; SS, Sjögren's syndrome; SJS, Stevens–Johnson syndrome; OD, right eye; OS, left eye; U, upper; L, lower; SD, standard deviation; LogMAR; logarithm minimum angle of resolution; yr, year
*A case of recanalization in lower punctum at five months after the surgery, and the additional surgery was performed by same surgical method. Data were included through the first and the second surgeries.

Table 2. Objective findings of the patients.

Case	Side	Fluorescein staining				tBUT		STT		VAS score	
		Adea		Density							
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	Right	2	1	2	1	4	5	9	9	5	3
2	Left	3	1	3	1	4	3	14	18	10	2
3	Right	1	0	1	0	1	2	1	1	10	7
	Left	3	1	3	1	1	3	1	1	10	8
4	Right	3	1	3	1	1	1	5	7	6	1
	Left	3	1	3	1	1	1	5	9	6	1
5	Right	3	1	3	2	1	1	5	7	8	0
	Left	3	2	3	2	1	1	3	6	8	0
6	Right	3	1	3	2	2	2	1	7	10	0
	Left	1	1	1	1	3	3	1	7	10	0
7	Left	2	1	3	1	0	1	0	1	8	2
Mean ± SD		2.5 ± 0.8	1.0 ± 0.4	2.5 ± 0.8	1.2 ± 0.6	1.7 ± 1.3	2.1 ± 1.3	4.1 ± 4.3	6.6 ± 4.9	8.3 ± 1.9	2.2 ± 2.8
P-value		0.00003		0.0002		0.096		0.004		0.0002	

tBUT, tear break up time; STT, Schirmer's tear test; VAS, visual analogue scale; UNC, University of North Carolina; SD, standard deviation

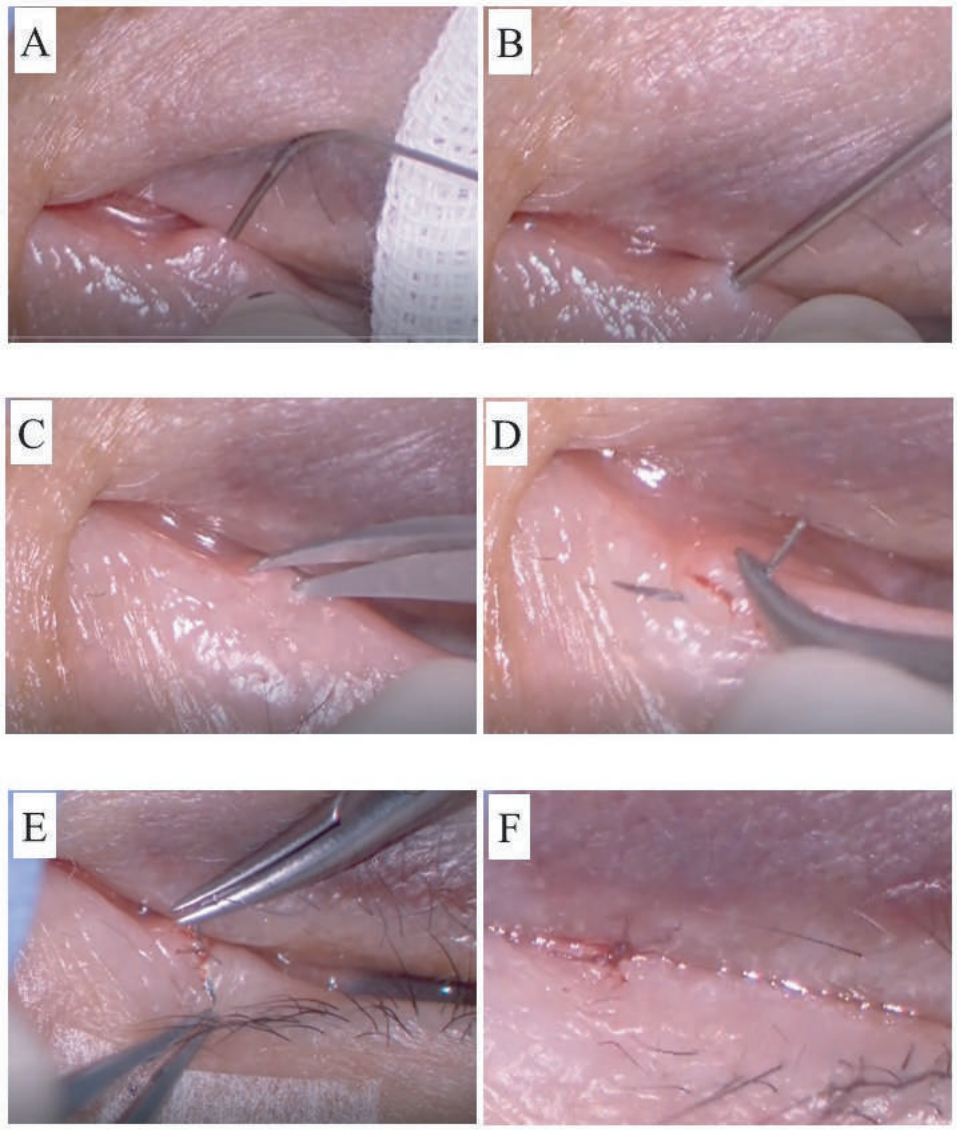

Figure 1. Images of surgical procedure. (A) Injection of Lidocaine into the punctum. (B) Punctal and cauterization of lacrimal canaliculi and puncta by diathermy. (C) Incision of the ring-shaped annulus fibrosus around the lacrimal punctum with a micro-scissor. (D) Suturing of lacrimal punctum with 8-0 Vicryl. (E) Second suture for cross-stitches. (F) Ligation was completed.

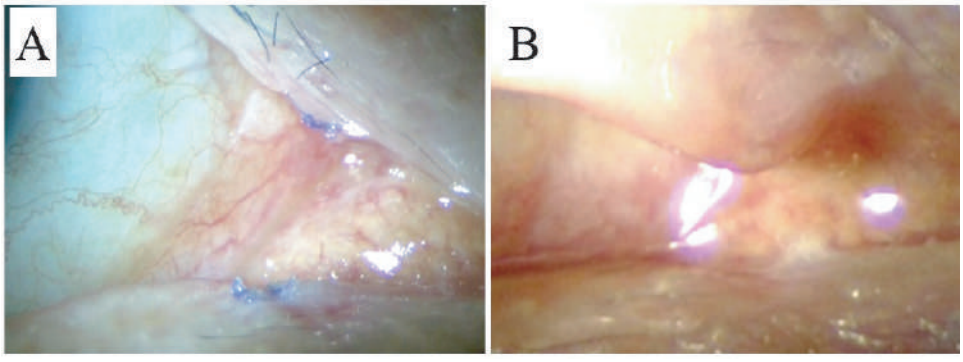

Figure 2. Postoperative images of case 1. Right eye of 69-year-old male. (A) Ligations were shown in both upper and lower lacrimal puncta at postoperative day 10 and were then removed. (B) After removal of suture. Lacrimal puncta were closed.

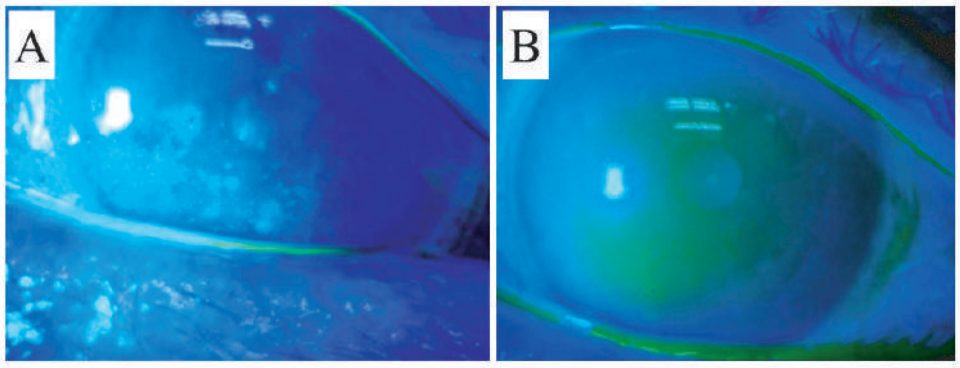

Figure 3. Microscopic images of case 1 after instillation of fluorescein eyedrops. (A) Fluorescein staining image prior to the surgery. The AD score was A2D2. Corrected visual acuity was 0.8 in Snellen chart. (B) Fluorescein image at postoperative day 14. No staining was shown. The AD score was A0D0. Corrected visual acuity was 1.2 in Snellen chart.

solution was instilled four times a day for one week. The absorbent thread was removed only if damage was seen on the surface of the eye [Figure 2].

Endpoints

The recorded data included patient characteristics, including diagnosis; corrected visual acuity before and after the operation, assessed by converting Snellen visual acuity into the Logarithm of the Minimum Angle of Resolution value (LogMAR); corneal staining score according to the AD classification,[24] which semi-quantitatively determines the area (A) and density (D) of fluorescein staining on a 3-point scale; tBUT; tear secretion volume assessed by the Schirmer tear test (STT); subjective symptoms assessed by the University of North Carolina (UNC); Dry Eye Management Scale,[25] intraoperative and postoperative complications; the presence or absence of recanalization after surgery; and any differences in eye drop use before and after the operation. The data were retrospectively reviewed based on the information in the medical records.

Statistical Analysis

Results are presented as means ± standard deviations and ranges. The pre- and postoperative values of items were statistically compared by Student's paired *t*-test. A *P*-value < 0.05 was considered as statistically significant.

RESULTS

The study participants comprised 11 eyes of seven patients (five eyes of three men and six eyes of four women), including 20 puncta (9 upper and 11 lower puncta). The mean age at surgery was 52.4 ± 14.3 years (range, 36–81 years), and the mean follow-up period was 12.7 ± 0.8 months (range, 12.1–14.4 months) [Table 1]. The diagnoses were as follows: primary Sjogren's syndrome – two patients, three eyes; Sjogren syndrome secondary to rheumatism – one patient, two eyes; depression – one patient, one eye; schizophrenia – one patient, two eyes; and Stevens–Johnson syndrome – one patient, two eyes. Two eyes of one patient with four puncta with Sjogren syndrome comprised reoperation after recanalization by cautery of puncta [Table 2]. During the one-year postoperative follow-up period, recanalization was observed in one eye with one puncta in one patient (5.0%) five months after the operation; the operation was repeated by the same surgical method, and the second postoperative result was favorable. The findings in this patient one year after the first surgery and six months after the second surgery were aggregated.

The corrected visual acuity converted to the LogMAR value significantly improved after the operation (0.326 ± 0.423 before vs 0.168 ± 0.321 after; $P = 0.019$; paired *t*-test) [Table 2]. The corneal staining A score also significantly improved (2.4 ± 0.8 before vs 1.0 ± 0.4 after; $P = 0.00003$; paired *t*-test), as did the D score (2.5 ± 0.8 before vs 1.1 ± 0.5; $P = 0.0003$; paired *t*-test). The images of typical improved case is shown in Figure 3. STT values significantly improved (4.1 ± 4.3 mm

before vs 6.6 ± 4.9 mm after; P = 0.004) too. No significant difference was seen in BUT (1.7 ± 1.3 s before vs 2.1 ± 1.3 s after; P = 0.167), but subjective symptoms showed a significant improvement (8.3 ± 1.9 before vs 2.2 ± 2.8 after; P = 0.015). No intraoperative complications were observed. Postoperative complications included keratitis due to suture contact with the cornea one week after surgery (9.1%) in one eye in one patient; the infiltration was healed one week later after treatment with antibacterial eye drops.

DISCUSSION

According to previous reports, the success rate of lacrimal canaliculi ablation for severe dry eye varies from 14% to 100% because the punctum and canaliculi can show recanalization after punctal closure; the cause of recanalization is unknown, however, it is assumed that the punctum and canaliculi are not sufficiently adhered.[10] Therefore, several techniques have been developed to reduce the rate of recanalization.[10–23] A 65% success rate has been reported when a square of skin is cut out at the punctal opening, rotated by 180° and reinserted so that the skin covering the punctal opening no longer has an opening.[10] The success rate is 92% for canaliculi epithelial destruction by a drill and punctal suturing,[11] and 100% for closing the lacrimal punctum with a patch,[12] canaliculectomy,[13] or transfer of lacrimal punctum to dry dock.[14] However, the higher the success rate, the more invasive the surgical procedure is.[10] One of the greatest drawbacks of surgical punctal closure is that it is an open, invasive operation. Other new surgical techniques include first removing and reinserting a square of skin at the punctal opening, as described above,[10] and then closing the punctal opening with the semi-lunar fold of the bulbar conjunctiva. However, this approach is also relatively invasive. The aforementioned surgical techniques have the common goal to maintain the closure of the punctum so that it does not reopen. However, because all these techniques are relatively invasive, we developed an improved method for punctal closure[23] in patients with severe dry eye in which we combined lacrimal ablation and punctal suturing.

This study evaluated a novel, minimally invasive approach to surgical punctal occlusion that more reliably destroyed the canaliculi epithelium by performing ablation over the entire length of the canaliculi within the range in which the diathermy needle could be inserted and by using a new suturing method. The operation achieved significant improvements in objective and subjective variables. Previous studies[10–21] also performed ablation over the entire length of the canaliculi, but unlike the approach in our study, they did so with a high heat energy laser.[21] In the present study, we made an incision in the annulus fibrosus around the ring-shaped lacrimal punctum, with a scalpel parallel to the eyelid margin. We sutured end to end with cross-stitches across the punctum; our aim was to perform tight suturing. As a result, recanalization was observed in only one eye in one patient at month five, and recanalization did not occur in any other eyes up to one year. This recanalization rate of 5.0% was comparable or better than that of previous reports, indicating that our technique was more effective in closing the punctum. Because we considered that the postoperative inflammatory reaction might lead to adhesion of the canaliculi destruction site, we used an absorbent thread for suturing and did not use anti-inflammatory eye drops after the operation.

The advantage of our surgical procedure is that it does not require any special equipment and can be performed with a commercially available diathermy needle, standard suture thread, and general ophthalmic surgical equipment. The disadvantage is the risk of keratitis due to suturing. In our study, keratitis occurred in one eye in the early postoperative period, but we believe that it might have been avoided if the suture thread had been kept away from the cornea.

In the group of patients who underwent surgery with this surgical technique, tBUT and Schirmer levels did not significantly improve, but corrected visual acuity and corneal staining score did. In contrast to these inconsistent results, some studies reported that all these objective variables improved. We suggest that the Schirmer level may not have improved in our study because although our surgical technique increased tear retention in the meniscus after surgery, it did not affect tear secretion itself. Subjective symptoms improved with our new surgical approach. Considering that the latest dry eye diagnostic criteria place more emphasis on the presence of subjective symptoms,[1–4] this finding appears to be of great significance.

For patients with severe dry eye in whom it is difficult to insert a punctal plug or who experience repeated loss of punctal plugs, the method of punctal closure by lacrimal canaliculi cauterization and punctal suturing presented here appears to be an effective and minimally invasive treatment option. Additional studies that evaluate the long-term prognosis in larger sample sizes are warranted.

Financial Support and Sponsorship

This work was supported in part by a Grant-in-Aid for Special Research in Subsidies for ordinary expenses of private schools from the Promotion and Mutual Aid Corporation for Private Schools of Japan.

Conflicts of Interest

There are no conflicts of interest.

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Original Article

Effect of Phacoemulsification on Intraocular Pressure in Eyes with Functioning Tube Shunts

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Abstract

Purpose: To evaluate the effect of phacoemulsification on intraocular pressure (IOP) in eyes with functioning tube shunts.
Methods: This was a retrospective chart review of primary open-angle glaucoma (POAG) patients with a functioning tube who underwent phacoemulsification and had ≥24 months of follow-up. The primary end point was defined as surgical failure (IOP > 21 mmHg) at month 24, progression to no light perception (NLP) vision, glaucoma reoperation, or implant removal. Surgical failure defined as IOP >18 and >15 mmHg, changes in visual acuity (VA), IOP, and number of medications were assessed.
Results: Twenty-seven eyes of 27 patients with moderate or severe POAG were included. The mean age of the patients was 64.2 ± 10.8 years. The interval between the tube shunt and phacoemulsification was 28.8 ± 25.0 months. At the end of the study, four (14.8%) eyes met the failure criteria; the average time to failure was 9.3 ± 3.8 months. The causes of failure were high IOP in two (50.0%) and glaucoma reoperation in two (50.0%) eyes; however, no eyes progressed to NLP vision. Surgical failure defined as IOP >18 and >15 mmHg showed an increasing failure rate (18.5% and 48.5%, respectively). The mean IOP and medications number remained stable at month 24 compared to baseline (P = 0.131 and P = 0.302, respectively). Initially, VA showed improvement, with the greatest improvement at 6 months (P = 0.001), but at 24 months the improvement was no longer significant (P = 0.430).
Conclusion: Phacoemulsification in patients with functioning tubes did not change the mean IOP in most of the patients (86.2%); the number of medications also did not increase.

Keywords: Cataract Extraction; Glaucoma Drainage Implants; Intraocular Pressure; Phacoemulsification

J Ophthalmic Vis Res 2023; 18 (2): 150–156

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Received: 25-10-2021 Accepted: 30-08-2022

Access this article online

Website: https://knepublishing.com/index.php/JOVR

DOI: 10.18502/jovr.v18i2.13180

How to cite this article: Shalaby WS, Patel P, Lam SS, Ganjei A, Shukla AG, Kolomeyer N, Lee D, Katz LJ, Moster MR, Myers J, Razeghinejad R. Effect of Phacoemulsification on Intraocular Pressure in Eyes with Functioning Tube Shunts . J Ophthalmic Vis Res 2023;18:150–156.

INTRODUCTION

Cataract surgery in patients with preexisting glaucoma or glaucoma surgery is challenging considering the potential impairment of postoperative intraocular pressure (IOP) control. The development of cataract after glaucoma surgery is not uncommon.[1] It has been suggested that intraocular inflammation during and after cataract surgery may result in scarring and fibrosis of the filtering trabeculectomy blebs.[2] Similarly, the inflammatory cells and mediators may cause fibrosis around the shunt reservoir.[3] However, there is no definite evidence supporting this theory. Several studies have investigated the effect of cataract surgery on trabeculectomy blebs. There have been mixed results on the bleb survival. While some studies showed increased failure of trabeculectomy and IOP elevation,[4--7] others reported no effect.[8--10] The literature on the effect of cataract extraction in eyes with prior tube shunts is limited.[3, 11, 12]

Prior studies showed lack of change in IOP and medications number in functioning tubes following phacoemulsification; however, they had a limited sample size, variable follow-up duration, and heterogenous type of glaucoma.[3, 11, 12] The study aimed to investigate the survival of tube shunts after phacoemulsification in patients with primary open-angle glaucoma (POAG).

METHODS

This single-center retrospective case series was performed at a tertiary eye care center. The study protocol was reviewed and approved by the Institutional Review Board of Wills Eye Hospital, Philadelphia, PA, United States; and the approval number was [19-857]. The study was conducted in accordance with the Health Insurance Portability and Accountability Act regulations. The study protocol adhered to the tenets of the Declaration of Helsinki and the guidelines for human studies. As this was a retrospective study with de-identified data, informed consent was not required. The medical records of consecutive patients diagnosed with POAG who were treated with tube shunts including the Ahmed glaucoma valve (AGV; New World Medical Inc., Rancho Cucamonga, CA, USA) or the Baerveldt glaucoma implant (BGI; Advanced Medical Optics, Santa Ana, CA, USA) followed by phacoemulsification between 2008 and 2018 were reviewed.

Patients aged 18 years or older who had undergone successful tube shunt surgery for POAG with IOP $\leq$ 21 mmHg, with or without medications, followed by phacoemulsification were included. Exclusion criteria were angle closure, neovascular, or inflammatory glaucoma, cataract extraction by any technique other than phacoemulsification, phacoemulsification combined with any glaucoma surgery, or a follow-up of less than two years after phacoemulsification. In patients with both eyes meeting the inclusion criteria, only the first eye was included.

Visits at baseline, postoperative day 1, week 1, months 1, 3, 6, 12, 18, and 24 after the cataract surgery were reviewed. Demographic data such as age and sex, and medical and surgical history were collected. Preoperative clinical data included best-corrected visual acuity (BCVA), IOP, topical glaucoma medications, and cup/disc ratio (CDR) at three consecutive visits prior to phacoemulsification. Postoperative data included BCVA, IOP, glaucoma medications, CDR, postoperative complications, and need for additional glaucoma surgery.

The primary outcome measure was the cumulative rate of surgical failure at 24 months. Surgical failure was defined as IOP > 21 mmHg with medications at two consecutive visits, progression to no light perception (NLP) vision, and glaucoma reoperation including second tube shunts, cyclophotocoagulation, or removal of the existing tube shunt. Changes in VA, IOP, glaucoma medications, and CDR at month 24 were compared to baseline. Additionally, analyses of surgical failure defined as IOP >15 and >18 mmHg were performed.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 27.0 (IBM Analytics, Chicago, IL, USA). Snellen VA measurements were converted to logarithm of the minimum angle of resolution (logMAR) equivalents for the purpose of data analysis. Continuous variables were presented as mean $\pm$ standard deviation. Proportions (%) were used to describe categorical variables. Paired sample *t*-tests were used to compare continuous variables within the same group. *P*-values <

0.05 were considered as significant. Kaplan–Meier survival analysis with log-rank tests were used to assess the survival.

RESULTS

Twenty-seven eyes of 27 patients were included in this study (16 AGV and 11 BGI). Baseline patient characteristics are shown in Table 1. The mean age was 64.2 ± 10.8 years, and 16 (59.3%) patients were females. All patients had moderate to severe glaucoma. Six patients (22.2%) had prior trabeculectomy before the tube shunt surgery. The mean LogMAR VA, IOP, and number of glaucoma medications were 0.94 ± 0.92, 16.0 ± 4.7 mmHg, and 2.4 ± 1.5, respectively. The average interval between tube shunt surgery and phacoemulsification was 28.8 ± 25.0 months.

At month 24, a total of four (14.8%) eyes met the failure criteria. Failure occurred at 19.3 ± 3.8 months after cataract extraction. Reasons for failure were high IOP in two (50.0%) eyes and glaucoma reoperation in two (50.0%) others. No eye progressed to NLP vision. Higher failure rate was observed with the surgical success defined as IOP <18 and <15 mmHg (18.5% and 48.5%, respectively). The rate, reasons, and time to failure with the three failure criteria are shown in Table 2. Kaplan–Meier survival analysis showing the cumulative rate of surgical failure at 24 months using the three failure criteria is displayed in Figure 1.

Visual acuity improved after surgery and the difference with baseline was statistically significant at month six, with an improvement in logMAR VA of 0.41 ± 0.54 units (P = 0.001), but not at month 24 (0.11 ± 0.67-unit improvement, P = 0.430). No eyes progressed to NLP vision.

Baseline and follow-up IOPs are presented in Figure 2. Patients who met the failure criteria due to reoperation for glaucoma implant removal or progression to NLP vision were censored in statistical analysis of the follow-up visits. At postoperative day one visit, IOP was higher compared to baseline (18.1 ± 6.2 mmHg vs 16.0 ± 4.7 mmHg, P = 0.053). Then, a tendency for lower IOP as compared to baseline was observed at all follow-up visits, but not statistically significant (P > 0.05), except in the third month at which IOP was significantly lower compared to baseline (13.0 ± 3.7 mmHg vs 16.0 ± 4.7 mmHg, P = 0.011). At month 24, the IOP was lower by 1.6 ± 5.1 mmHg compared to baseline (P = 0.131).

Figure 3 shows the number of glaucoma medications at baseline and follow-up. A decremental trend for the number of glaucoma medications was observed at all time points; however, it was statistically significant at postoperative months 6 and 12 compared to baseline (P = 0.02 and P = 0.016, respectively). At month 24, the mean number of medications was 0.3 ± 1.5 lower compared to the baseline (P = 0.302).

Hyphema (1 [3.7%]), IOP spikes (IOP elevation ≥ 10 mmHg from the baseline) (1 [3.7%]), and inflammatory reaction (>+1 cells in the anterior chamber) (14 [51.9%]) were the early postoperative complications; all resolved with conservative management. No eyes developed persistent corneal edema. During the follow-up period, one eye (3.7%) required tube revision and two (7.4%) eyes received second tube shunt.

DISCUSSION

Our study shows that the mean IOP and number of glaucoma medications remained stable for two years following cataract extraction in POAG patients with a functional tube shunt. The rate of surgical failure was 14.8%, 18.5%, and 48.5% at IOPs of >21, <18, and <15 mmHg, respectively. While the effect of cataract surgery on the trabeculectomy function has been heavily studied,[4–10] there are limited studies on the tube shunts, and all have included various forms of open-angle glaucoma.[3, 11, 12]

Gujral et al[12] retrospectively investigated the outcomes of phacoemulsification in eyes with functioning AGVs. The study included 23 eyes of 19 patients with an average follow-up of 1.6 ± 0.6 years after the cataract surgery. Similar to our study, the mean IOP and number of medications did not change after phacoemulsification (P > 0.05 for both). However, the follow-up in our study was longer. The pattern of postoperative IOP change was similar to our study; increased from 14.5 ± 3 mmHg (preoperative) to 19.2 ± 6.3 mmHg on postoperative day one, declined at month one, and remained stable afterward. The surgical failure defined as IOP >21 mmHg was observed in two (9%) eyes and one of them (4.0%) underwent second tube shunt. These

Table 1. Baseline Characteristics of Patients with Phacoemulsification and Prior Tube Shunt Surgery.

Number of eyes	27
Number of patients	27
Age, yr	64.2 ± 10.8
Sex, Females: *N* (%)	16 (59.3)
Surgical eye, Right: *N* (%)	16 (59.3)
Baseline visual acuity: LogMAR	0.94 ± 0.92
Baseline intraocular pressure: mmHg	16.0 ± 4.7
Baseline medications number	2.4 ± 1.5
Baseline cup/disc ratio	0.7 ± 0.2
Glaucoma severity: *N* (%)	
Moderate	11 (40.7)
Severe	16 (59.3)
Glaucoma intervention prior to tube shunt surgery	
None	13 (48.1)
Selective laser trabeculoplasty	8 (29.6)
Trabeculectomy	6 (22.2)
Duration between tube shunt surgery and phacoemulsification: Months	28.8 ± 25.0

Table 2. Month 24 failure in patients with phacoemulsification and prior tube shunt surgery.

Failure criteria 1: IOP > 21 mmHg	
Failure: *N* (%)	4 (14.8)
Reasons of failure: *N* (%)	
IOP > 21 mmHg	2 (50.0)
Reoperation for glaucoma	2 (50.0)
Progression to NLP	0 (0.0)
Time to failure: Months	19.3 ± 3.8
Failure criteria 2: IOP > 18 mmHg	
Month 24 failure: N (%)	5 (18.5)
Reasons of failure: N (%)	
IOP > 18 mmHg	3 (60.0)
Reoperation for glaucoma	2 (40.0)
Time to failure: Months	17.8 ± 7.6
Failure criteria 3: IOP > 15 mmHg	
Month 24 failure: N (%)	13 (48.1)
Reasons of failure: N (%)	
IOP > 15 mmHg	11 (84.6)
Reoperation for glaucoma	2 (15.4)
Time to failure: Months	12.6 ± 7.2

IOP, intraocular pressure; NIP, no light perception

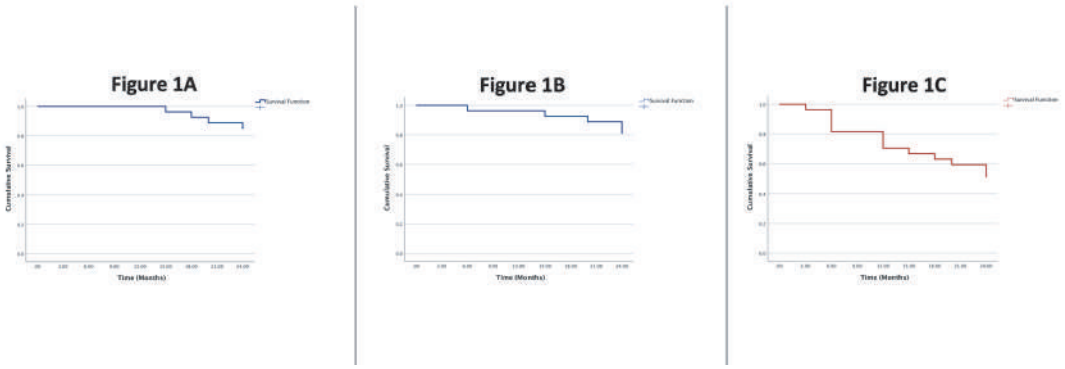

Figure 1. Kaplan–Meier Survival Plot of cumulative probability of surgical failure in patients with phacoemulsification and prior tube shunt surgery. Surgical failure was defined as intraocular pressure >21 mmHg (1A), >18 mmHg (1B), or >15 mmHg (1C).

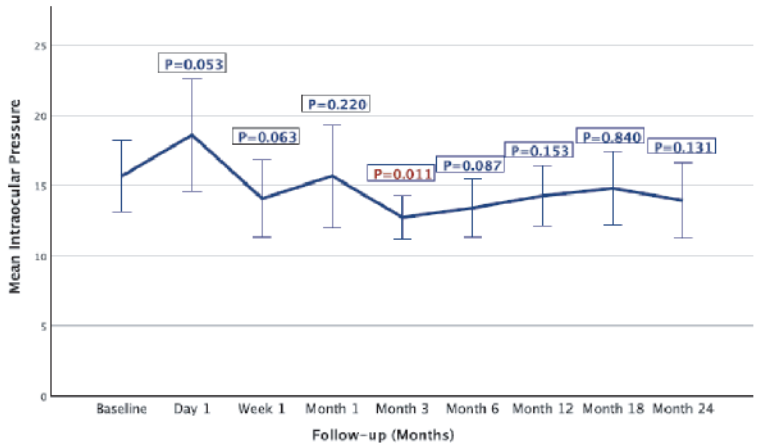

Figure 2. Intraocular pressure changes over time in patients with phacoemulsification and prior tube shunt surgery. Intraocular pressure remained stable through two years following phacoemulsification. Significant reduction was observed at month three (*P* = 0.011).

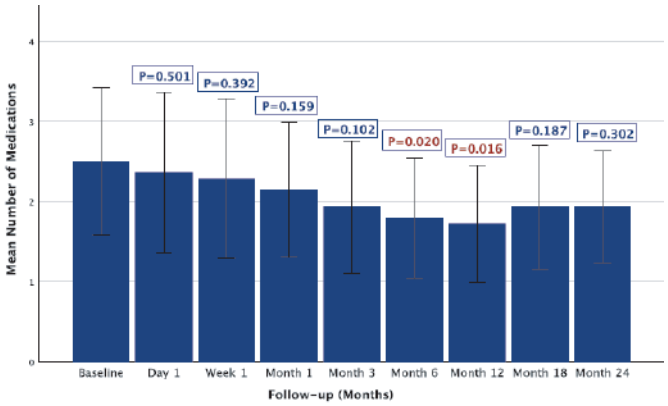

Figure 3. Medication number changes over time in patients with phacoemulsification and prior tube shunt surgery. Medication number remained stable through two years following phacoemulsification. Significant reduction was observed at month six (P = 0.020) and month 12 (P = 0.016).

findings were comparable to our failure (14.8%) and reoperation (7.4%) rates. On the other hand, more eyes experienced IOP spikes at day one postoperatively (17.0%) compared to ours (3.7%).

Erie et al[3] retrospectively studied the effects of phacoemulsification on nine eyes of eight patients with a functioning BGI with an average follow-up of 21.0 ± 3.0 months. The mean IOP and number of medications did not change significantly at the last follow-up visit (P = 0.830 and P = 0.170, respectively). Only one eye required second glaucoma surgery.

In another retrospective study, 11 eyes of 11 patients with double plate Molteno shunt (8), single plate Molteno shubt (2), or BGI (1) were followed for 21.0 ± 27.0 months following cataract surgery.[11] Phacoemulsification was performed in eight eyes and extracapsular cataract extraction was done in three eyes. No significant difference was observed between the mean IOP and the number of medications before and after cataract extraction (P = 0.850 and P = 0.440, respectively). Three eyes had IOP >21 mmHg and only one of them required glaucoma surgery.

Although VA improved in the first six months, the vision was not statistically different from baseline at month 24. This is consistent with prior studies, although in some studies it was attributed to corneal edema.[11, 12] Corneal edema was not observed in our study. Posterior capsule opacification could be a potential cause for the lack of change in vision after cataract extraction.

The high IOP at day one may be related to the postoperative period IOP spikes following cataract surgery due to viscoelastic agents.[13, 14] The IOP decline afterward could be because of the IOP-lowering effect of phacoemulsification in glaucomatous eyes.[15, 16] The mechanism is not clear, but may be related to widening of the anterior chamber angle, decreased aqueous production by the ciliary body due to capsular bag contraction, or increased aqueous outflow due to trabecular meshwork stretching.[15–17]

The results of our study are in line with other studies on IOP profile following cataract extraction in patients with a functional tube, but the results on trabeculectomy are controversial. Some studies showed that phacoemulsification increased the surgical failure of trabeculectomy,[4–7] and others found no effect on bleb survival.[8–10] The mechanisms of IOP elevation following cataract surgery in those with a functional filtering surgery (trabeculectomy or tube shunts) seems to be similar. Inflammatory cells and cytokines released following cataract surgery may cause scarring of the filtering bleb.[2, 11]

The average duration between tube shunt surgery and phacoemulsification in this study was variable (28.8 ± 25.0 months). It is known that the time interval between the two surgeries may have prognostic ramifications. It is recommended to postpone the cataract surgery following filtering surgery as long as possible, without compromising patient's quality of life. A six-month gap between filtering surgery and the subsequent cataract extraction increases the chances of bleb survival.[18]

The patients in our study had phacoemulsification 28.8 months after shunt surgery and were followed for 24 months (about five years after shunt surgery). The failure rate in these patients was comparable with the rate reported in Ahmed Baerveldt Comparison (ABC) and Ahmed versus Baerveldt (AVB) studies.[19, 20] These findings confirm that phacoemulsification, at least, had no negative impact on the survival of tube shunts. However, such comparisons cannot conclude that phacoemulsification may augment the IOP-lowering effect of tube shunts, giving the different follow-up duration and the inclusion of secondary and refractory glaucoma types in the ABC and AVB studies.[19, 20]

Our study has several limitations. There were no preset criteria for the addition of medications or preforming another surgery and has been at the discretions of surgeons. This is the universal issue with all retrospective studies. Additionally, the sample size was small as only POAG patients with a complete two-year follow-up were included. The follow-up period in our study was longer than prior studies and contrary to them we included only one eye of each patient and only POAG cases. Compared to all prior studies we had the largest sample size (27 vs 9, 11, and 23 eyes), and all patients were followed-up for at least for 24 months.[3, 11, 12] Furthermore, both valved (AGV) and non-valved (BGI) tubes were included in this study which makes the results closer to the real-world practice.[19, 20]

In summary, the current study showed that POAG patients with functioning tube shunts can maintain IOP control after phacoemulsification, suggesting that cataract surgery may not have a negative impact on the survival of tube shunts.

Financial Support and Sponsorship

None.

Conflicts of Interest

None.

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Original Article

How Many Fenestrations Should I Make When Placing a Baerveldt Glaucoma Implant? A Laboratory Study

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Abstract

Purpose: This study investigates the effect of one versus two fenestrations on both fluid egress and opening pressure from a non-valved glaucoma implant.

Methods: In this laboratory study, we used an *in vitro* closed system comprised of ligated silicone tubing connected to a fluid reservoir and manometer to simulate the tubing found in a Baerveldt glaucoma drainage implant. Fenestrations were created using an 8-0 Vicryl TG140-8 suture needle. Main outcome measures included volume of fluid egress and fenestration opening pressures, which were measured via micropipette and increasing pressure until fluid egress was observed.

Results: No significant difference was observed in fluid egress between tubing with one versus two fenestrations at pressures ≤40 mmHg. At 50 mmHg, a statistically significant difference was observed in fluid egress between tubing with one versus two fenestrations ($P < 0.05$). The first fenestration opened at 10.5 ± 3.77 mmHg and the second fenestration opened at 28.83 ± 5.09 mmHg (average ± standard deviation).

Conclusion: Our *in vitro* findings suggest there may exist a critical pressure >40 mmHg at which the second fenestration starts to play a significant role in fluid drainage. There may be no difference in the amount of fluid egress and effect on intraocular pressure between one or two tube fenestrations when preoperative intraocular pressure is ≤40 mmHg.

Keywords: Baerveldt; Drainage Implants; Fenestration; Glaucoma; Opening Pressure

J Ophthalmic Vis Res 2023; 18 (2): 157–163

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Received: 08-11-2022 Accepted: 12-01-2023

Access this article online

Website: https://knepublishing.com/index.php/JOVR

DOI: 10.18502/jovr.v18i2.13181

How to cite this article: Yang MC, Yang CD, Lin KY. How Many Fenestrations Should I Make When Placing a Baerveldt Glaucoma Implant? A Laboratory Study. J Ophthalmic Vis Res 2023;18:157–163.

INTRODUCTION

In the recent years, glaucoma drainage implants (GDIs) have become a mainstay in surgical glaucoma management becoming the preferred option over trabeculectomy in a growing number of glaucoma practices.[1] GDIs share a common anatomy comprising of a silicone tube connected to an endplate. The silicone tube is surgically inserted into the eye to allow access to the aqueous humor, and the endplate is fixed to the sclera and covered with conjunctiva and Tenon's capsule. Like trabeculectomy, GDIs are considered penetrative glaucoma surgeries that create a *de novo* pathway for aqueous drainage.

The two most common GDIs on the market are the Ahmed glaucoma drainage implant (AGI; New World Medical, Rancho Cucamonga, California) and the Baerveldt glaucoma drainage implant (BGI; Johnson & Johnson, Santa Ana, California). When compared to the AGI, the BGI results in a significantly lower mean intraocular pressure (IOP) with lower rates of failure. However, the BGI carries a higher risk of postoperative hypotony, in part because it does not have a valve mechanism.[2, 3] Valved implants generally have a pressure floor below which aqueous flow through the implants is disabled. The Krupin implant utilizes a unidirectional valve that opens when IOP is >11 mmHg.[4] The valve mechanism of the AGI involves thin silicone membranes that open, via the Venturi effect, when IOP is >8–12 mmHg.[5] On the other hand, non-valved implants, like the BGI, allow for unrestricted flow of aqueous humor and rely on encapsulation around the endplate for flow resistance.[6] For this reason, flow through non-valved glaucoma implants must be restricted in the immediate postoperative period before encapsulation has occurred. One common restriction method is to ligate the silicone tube with dissolvable suture. It is common practice to fenestrate the ligated tubes to allow for some degree of aqueous humor drainage while the capsule is maturing.[6]

Little consensus exists regarding the number and manner with which fenestrations are created in non-valved GDIs. Similarly, no heuristics exist to guide how fenestrations should or should not be modified based on preoperative IOP. Such heuristics, even if theoretical or based on *in vitro* observations, are nevertheless important because they may help guide clinicians to achieve a more stable and predictable IOP during the immediate postoperative period. Moreover, only a few published experiments evaluating the number of fenestrations and their effects on outflow facility and IOP in *in vitro* and *ex vivo* systems have been performed, with equivocal results.[7, 8] In an *in vitro* study of a ligated BGI with four fenestrations using a 7-0 Vicryl TG140-8 needle, the volume of fluid egress was found to positively correlate with simulated IOP.[8] In an *ex vivo* study of porcine eyes, three fenestrations with a 7-0 Vicryl TG140-8 needle led to a significantly lower final IOP compared to a single fenestration after 15 min with an initial IOP of 50 mmHg.[7] Additional studies are needed to evaluate the wide spectrum of fenestration possibilities and their effects on fluid egress.

In our study, we utilize an *in vitro* apparatus as a model for ligated BGI tubing to evaluate fluid efflux with one versus two fenestrations created with a Vicryl TG140-8 needle at discrete intra-tubular pressures. In addition to quantifying the volume of fluid egress, we also identify an opening pressure at which fluid outflow begins from each fenestration. We hypothesized that the number of fenestrations in the tubing does not significantly affect the volume of fluid efflux until a critical intra-tubular pressure threshold is reached.

METHODS

Glaucoma Drainage Implant Experimental Apparatus

An *in vitro* experimental apparatus was created as a model for ligated BGI tubing [Figure 1]. Non-sterile silicone tubing (Access Technologies, 2 French silicone catheter, Model BC-2S), with an internal diameter of 0.3 mm and outer diameter of 0.6 mm, was used to simulate the silicone tubing attached to the Baerveldt glaucoma drainage implant (0.30 × 0.63 mm). The silicone tubing was connected to the system by a 27G cannula (Eagle Labs, 27ga × 1" cannula, Model 113-27NS) attached to a three-way stopcock (Medex, 3-Way Stopcock, Model MX4311L). The open end of the silicone tube was clamped with a hemostat to create a closed system. The other two ends of the three-way stopcock were attached to intravenous tubing (Baxter, Continu-Flo Solution Set, Model 2C8537s) with a 50 mL syringe as a fluid reservoir (BD, 50 mL syringe Luer-Lok Tip, Model 309653) and to

a manometer (Omega, absolute pressure meter, Model HHC281). The fluid reservoir was filled with a balanced salt solution (Alcon, BSS Sterile Irrigating Solution, Model 9012632-1115).

Tube Fenestration and Fluid Egress Measurement at Variable IOP

A simulated IOP (or intra-tubular pressure) was held constant at a predetermined level by adjusting the height of the fluid reservoir (20, 30, 40, and 50 mmHg). Tube fenestrations were created using a spatulated suture needle (Ethicon, 7-0 Vicryl, TG140-8 needle) by entering perpendicularly to the center of and passing through the front and far side of the tubing. The two fenestrations were approximately 1 mm apart. Two horizontal slit openings (parallel to the walls of the tube, front and far sides of the tube) were created with a single fenestration [Figure 2]. Two fenestrations resulted in four horizontal slit openings. Care was taken to enter and exit along the same needle path to avoid enlarging the fenestration. The total volume of egressed fluid was measured from both fenestrations after 5 min using Beta-Pette micropipettes to the nearest microliter. Four trial measurements were obtained for each experimental replicate; each trial was conducted with new silicone tubing and newly created fenestrations [Table 1]. A total of 32 trial measurements were obtained.

Opening Pressure Measurement

Simulated IOP (or intra-tubular pressure) was initially held at atmospheric pressure. Two fenestrations were then created in the manner as described in "Measuring the Volume of Fluid Egress at Variable IOP." Subsequently, the hydrostatic pressure was gradually increased by raising the reservoir height at an approximate rate of 1 mmHg per sec. The intra-tubular pressure was increased until both fenestrations were open. The opening pressure of the fenestration was defined as the pressure required to induce approximately 5 µl of fluid efflux, given that this volume of fluid would be visible underneath the microscope. Five trial measurements were obtained for each of the six experimental replicates; each replicate was conducted with new silicone tubing and newly created fenestrations.

Statistical Analysis

Data were recorded in an Excel spreadsheet and statistical analysis was performed with an unpaired Student's *t*-test like other studies comparing similar outcomes.[7] *P*-values < 0.05 were considered statistically significant. Imaging of the fenestrations were obtained with a digital camera (iPhone 12 Pro, Apple, Cupertino, United States) equipped with a microscope attachment (DIPLE Lux, SmartMicroOptics, Genoa, Italy).

RESULTS

In the 20-mmHg trial, a single fenestration resulted in a mean fluid egress of 113.5 µL, two fenestrations 159 µL; not significantly different with a *P*-value of 0.16 [Table 1]. In the 30-mmHg trial, a single fenestration resulted in a mean fluid egress of 188.25 µL, two fenestrations 263.5 µL; not significantly different with a *P*-value of 0.15. In the 40-mmHg trial, a single fenestration resulted in a mean fluid egress of 213.75 µL, two fenestrations 293.75 µL; not significantly different with a *P*-value of 0.08, but notably trending toward significance. In the 50-mmHg trial, a single fenestration resulted in a mean fluid egress of 247.75 µL, two fenestrations 548.75 µL; notably different with a significant *P*-value of 0.02.

Although mean fluid egress trended toward increasing with an additional fenestration, it was only statistically significant in the 50-mmHg group [Figure 3].

The first fenestration opened at 10.5 mmHg (range: 6–21 mmHg), while the second fenestration opened at 28.83 mmHg (range: 23–41 mmHg) with a *P*-value of < 0.001 [Table 2]. Notably, the first fenestration to open was not always the one closest to the fluid source.

DISCUSSION

The salient findings of our study are as follows: (1) at a simulated intraocular pressure of 50 mmHg, there is a statistically significant difference in total volume of egressed fluid from the silicone tube with one versus two fenestration(s); (2) there is no significant difference if simulated IOP is 40 mmHg or less (the 40 mmHg group was very close to being statistically significant with a *P*-value of 0.08); (3) in the opening pressure trials,

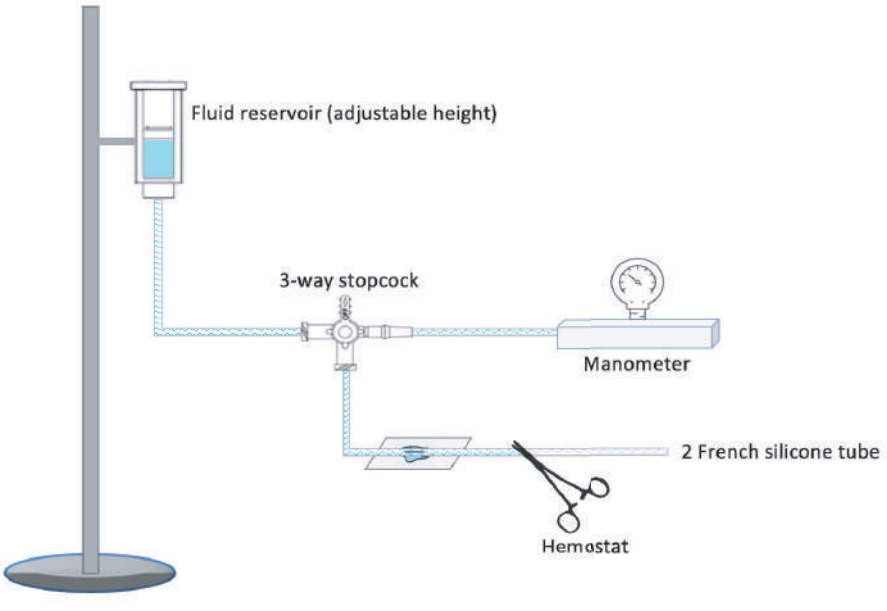

Figure 1. Diagram of *in vitro* experimental setup modeling a ligated silicone tube of a non-valved glaucoma drainage implant. Two French silicone tubing connected to a 27-gauge cannula attached to a three-way stopcock. The open end of the silicone tube was clamped with a hemostat. The other two ends of the three-way stopcock were attached to intravenous tubing with a fluid reservoir and to a manometer.

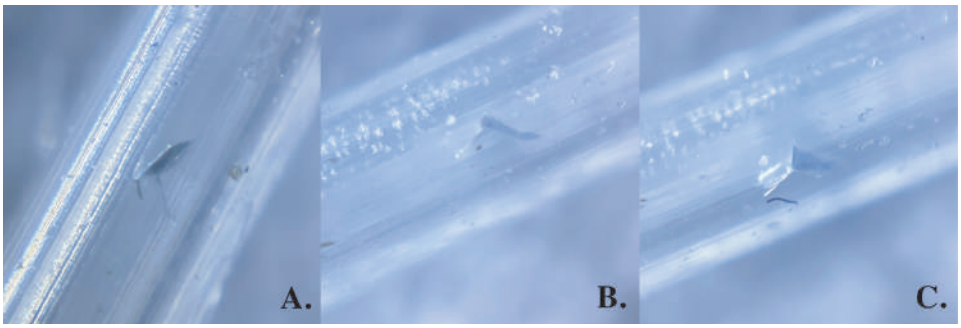

Figure 2. Microscopic images of fenestrations in silicone tubing. Fenestrations were created with 7-0 Vicryl on a TG140-8 spatulated needle. **(A)** Uniplanar fenestration structure. **(B)** Biplanar fenestration structure. **(C)** Triplanar fenestration structure.

the second fenestration opened at a pressure of 28.83 ± 5.09 mmHg. The last two observations suggest that a critical opening pressure exists between 40 and 50 mmHg beyond which the second fenestration significantly contributes to fluid drainage out of the silicone tube. It is possible that the critical pressure may actually exist at a pressure between 30 and 40 mmHg, given that the second fenestration opens at approximately 29 mmHg. These findings suggest that the creation of a second fenestration in the ligated Baerveldt tube does not result in a significant decrease in IOP if the preoperative IOP is <40 mmHg. In other words, single fenestration should be sufficient when the preoperative IOP is <40 mmHg. Our *in vitro* experiment may provide some guidance to glaucoma surgeons when deciding the number of fenestrations to create intraoperatively. Yet, given the inherent limitations of an *in vitro* study, the results reported here should be considered in the broader context of surgeons' clinical and surgical expertise.

Olayanju et al characterized the outflow facility of a tube system with constant intraocular pressure and fenestrated with varying needles and blades.[8] They found that the outflow facility (mL/min/mmHg) was mainly dependent on intraocular pressure and did not significantly change by external weight on

Table 1. Fluid egress from silicone tube with one versus two fenestrations at varying simulated intraocular pressures after 5 min. Fenestrations were created with 7-0 Vicryl on a TG140-8 spatulated needle.

Simulated intraocular pressure (mmHg)	Number of fenestrations	Mean fluid egress at 5 min (µL) ± standard deviation	Minimum fluid egress at 5 min (µL)	Maximum fluid egress at 5 min (µL)	P-value
20 mmHg	1	113.5 ± 23.3	82	130	0.156
	2	159 ± 83.5	87	235	
30 mmHg	1	188.25 ± 128.85	53	350	0.149
	2	263.5 ± 10.01	235	283	
40 mmHg	1	213.75 ± 87.18	135	295	0.083
	2	293.75 ± 75.66	235	380	
50 mmHg	1	247.75 ± 124.89	144	428	0.021
	2	548.75 ± 174.81	505	620	

*mmHg, millimeters of mercury; µL, microliters

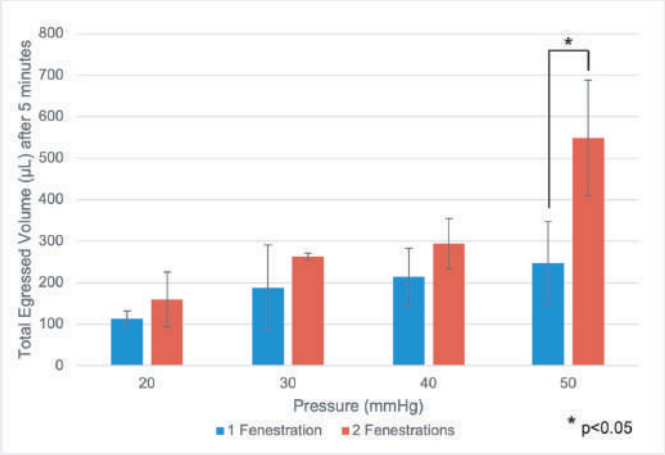

Figure 3. Fluid egress from silicone tube with one versus two fenestrations at varying simulated intraocular pressures after 5 min. Blue bar indicates one fenestration. Red bar indicates two fenestrations. Fenestrations were created with 7-0 Vicryl on a TG140-8 spatulated needle.
*mmHg, millimeters of mercury; µL, microliters

the tube (e.g., scleral patch graft). However, they made the observation that the microarchitecture of the fenestrations was widely variable; the same external forces (e.g., scleral patch graft) could either reinforce fenestration closure or hold the fenestrations open. The fenestrations created by the 7-0 Vicryl TG140-8 needle appeared to exhibit the lowest outflow facility when compared to openings created by a 15 blade and 9-0 nylon CS140-6 needle with a suture stent. However, the authors did not investigate differences in volume outflow between varying numbers of Vicryl needle fenestrations.

Honda et al utilized an *ex vivo* experimental set up with pig eyes and a syringe pump perfusing fluid into the system at the same rate as aqueous production (200 µL/hr).[7] Various needles were used to create one or three fenestrations (7-0 Vicryl, 7-0 PDS, 5-0 PDS, 3-0 PDS). After fenestrations were created, IOP was compared between needle types after 15 min of perfusion with a starting IOP of 50 mmHg. Only the 7-0 Vicryl group had a significantly lower final IOP between the one and three fenestration subsets. However, when comparing the IOP curves between tubes with one versus three fenestrations, the slope of IOP decline in the tube with three

Table 2. Opening pressure of first and second fenestration of silicone tube. Fenestrations were created with 7-0 Vicryl on a TG140-8 spatulated needle.

	Mean opening pressure ± standard deviation (mmHg)	Minimum opening pressure (mmHg)	Maximum opening pressure (mmHg)	P-value
Fenestration #1	10.5 ± 3.77	6	21	< 0.001 (1.76E-19)
Fenestration #2	28.83 ± 5.09	23	41	

*mmHg, millimeters of mercury; E, 10^x

fenestrations was steeper between approximately 35–50 mmHg. Interestingly, when IOP was < 35 mmHg, both tubes (one and three fenestrations) appeared to exhibit similar slopes of IOP decline. This suggests that Honda et al also identified a critical opening pressure (approximately >35 mmHg) at which the second and third fenestrations begin to significantly contribute to fluid drainage out of the tube. This critical opening pressure phenomenon may be explained by the elasticity of the silicone tubing. In the absence or insufficiency of an internal fluid load, hydrodynamic pressure cannot overcome the elasticity of the silicone, and the tube will self-seal.

Like other reports evaluating glaucoma tube shunt fenestrations, our results varied widely between each trial.[7, 8] This may be due to microscopic variations in surgical technique resulting in a variety of differences in microarchitecture between fenestrations [Figure 2]. We found that fenestrations with the 7-0 Vicryl TG140-8 needle could take the form of a uniplanar, biplanar, or triplanar structure. Certainly, other microarchitecture configurations are possible. It would be valuable to characterize the microstructure of each fenestration (e.g., uniplanar, biplanar, triplanar, etc.) and evaluate the differences in opening pressure and fluid egress of each microstructure type. Although our results do not consistently demonstrate this, other authors have found that multiple fenestrations lead to a wider standard deviation of results compared to a single fenestration.[7] Presumably, with an increased number of fenestrations, microarchitecture variability also increases. For example, the distance between each fenestration and the location of the fenestrations in relation to the scleral patch graft may affect opening pressure and/or fluid egress. Honda et al also found that round needles (e.g., PDS needles) allowed for more consistent fenestration construction and more predictable experimental outcomes,[7] further emphasizing the importance of fenestration microarchitecture.

The limitations of our study were that we utilized an *in vitro* experimental apparatus instead of pig or human eyes. Our model recapitulated a real eye but assumed no outflow via the traditional or uveoscleral pathways, and no peritubular flow. As with any *in vitro* model, our system does not perfectly mimic the normal physiology of aqueous drainage. To avoid variability in our measurements, we elected to hold the pressure at a constant level; however, in a human eye, IOP would decrease as aqueous exits. In other words, the physiologic flow rate would be dynamic and decelerate as the pressure falls below the opening pressures of the fenestrations. Additionally, we utilized balanced salt solution in place of aqueous humor. Prior studies have indicated that aqueous humor, with its various proteins and blood products, can occlude fenestrations.[9] Aqueous humor also has a different viscosity from balanced salt solution and, as such, the actual opening pressure of an implanted BGI may be slightly different; however, we posit that the relatively small contribution from the second fenestration in most of the IOP ranges tested still holds clinically. It is important to keep in mind that the critical pressures reported in this study are likely lower than what would be seen in patients; the effect of episcleral fibrosis was not accounted for in this study. Moreover, our model does not include a simulated scleral patch graft. In theory, the scleral patch graft may apply external pressure to the tubing, either facilitating flow or blocking the fenestrations.[8] However, prior studies (Olayanju et al) simulated the presence of the patch graft with external weights and found no significant difference in outflow facility of the tubing.

The apparent difference between our observed critical pressure (>40 mmHg) and the opening pressure of the second fenestration (approximately 30 mmHg) may be explained by the design of our fluid egress experiments, in which simulated IOP was increased in 10 mmHg intervals. These intervals do not precisely capture the pressure at which egress saturates. Future experiments can be performed to expand on our study by conducting experiments between the 10 mmHg intervals, determining the effect of interfenestration distance on opening pressure, studying the effect of fenestration numbers greater than two, and quantifying the microarchitecture of manually created fenestrations.

Our study demonstrates no significant difference in fluid outflow from two French silicone tubing between one or two fenestrations created by a 7-0 Vicryl TG140-8 needle at simulated IOPs ≤40 mmHg in an *in vitro* setting. The second fenestration has an opening pressure of approximately 29 mmHg but may not induce a significant effect on outflow until IOP is >40 mmHg. Our study is limited by several aforementioned factors which may restrict its translation to clinical practice in patients. However, assuming the egressed volume of fluid correlates with IOP, our findings suggest that the creation of more than one fenestration in BGI tubing may not have a significant effect on postoperative IOP unless preoperative IOP is >40 mmHg.

Financial Support and Sponsorship

KYL is a recipient of the Clinician Scientist Award from the American Glaucoma Society. The Gavin Herbert Eye Institute is a recipient of an unrestricted grant from Research to Prevent Blindness (RPB).

Conflicts of Interest

No conflicts exist for any author.

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Original Article

Ziv-aflibercept in Diabetic Macular Edema: Relation of Subfoveal Choroidal Thickness with Visual and Anatomical Outcomes

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Abstract

Purpose: To evaluate the effects of intravitreal ziv-aflibercept injections (IVZ) on subfoveal choroidal thickness (SCT) as well as on central macular thickness (CMT) and on best corrected visual acuity (BCVA) changes in eyes with center-involved diabetic macular edema (CI-DME).
Methods: Fifty-seven eyes of 36 patients with CI-DME were included in this prospective interventional case series. Structural optical coherence tomography (OCT) and enhanced depth imaging OCT were performed at baseline followed by three monthly 1.25 mg IVZ injections. Changes of SCT, CMT, and BCVA at each follow-up session were assessed. The association between baseline SCT and its monthly changes with final visual and anatomical outcomes were also assessed.
Results: CMT at baseline, and at the first, second, and third month follow-up sessions were 396 ± 119, 344 ± 115, 305 ± 89, and 296 ± 101 µm, respectively (*P*-value < 0.001). SCT at baseline, and at months one, two, and three were 236 ± 47, 245 ± 56, 254 ± 54, and 241 ± 54 µm, respectively (*P*-value > 0.99). Corresponding figures for BCVA were 0.58 ± 0.29, 0.47 ± 0.31, 0.4 ± 0.24, and 0.37 ± 0.23 LogMAR, respectively (*P*-value < 0.001). There was a statistically significant positive correlation between BCVA and CMT changes following IVZ injections (*P*-value < 0.001). However, there were no significant correlations between SCT changes and visual acuity (VA) and CMT changes following IVZ injections.
Conclusion: IVZ improved visual outcomes and macular thickness profiles in patients with CI-DME. However, IVZ had no significant effect on SCT. Baseline SCT and its monthly changes had no association with visual and anatomical outcomes.

Keywords: Center-involved Diabetic Macular Edema; Central Macular Thickness; Intravitreal; Subfoveal Choroidal Thickness; Ziv-Aflibercept

J Ophthalmic Vis Res 2023; 18 (2): 164–169

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Received: 25-10-2021 Accepted: 30-08-2022

Access this article online

Website: https://knepublishing.com/index.php/JOVR

DOI: 10.18502/jovr.v18i2.13182

How to cite this article: Moradian S, Soheilian M, Asadi M, Baghi A, Safi H, Abtahi S-H. Ziv-aflibercept in Diabetic Macular Edema: Relation of Subfoveal Choroidal Thickness with Visual and Anatomical Outcomes . J Ophthalmic Vis Res 2023;18:164–169.

INTRODUCTION

Diabetic macular edema (DME) is the main cause of vision loss in diabetic patients.[1, 2]. The use of anti-vascular endothelial growth factors (anti-VEGFs) is currently the main therapeutic choice for DME.[3] Ziv-Aflibercept (Zaltrap, Sanofi-Aventis US, LLC, Bridgewater, New Jersey, USA and Regeneron Pharmaceuticals, Inc, Tarrytown, New York, USA) is an FDA-approved drug for treatment of colorectal and metastatic cancers. As an analogue of aflibercept, ziv-aflibercept is a monoclonal antibody that binds to VEGF A and B of various isoforms and placental growth factor, which also possesses a good safety profile and is of lower cost.[4, 5] There is a growing body of evidence that intravitreal ziv-aflibercept (IVZ) improves visual outcomes and macular thickness profiles in patients with DME.[6–11] However, the changes of choroidal thickness in eyes with DME treated with IVZ and the effects of subfoveal choroidal thickness (SCT) on visual and anatomical outcomes remain unknown.

Subfoveal choroidal thickness measurement performed by enhanced depth optical coherence tomography (EDI-OCT) in DME cases treated with anti-VEGFs has been proposed as a predictor of therapeutic outcomes.[12] However, the correlation between baseline SCT and treatment responses in patients with DME remains controversial.[3, 13, 14] Thinning of SCT might aggravate retinal hypoxia and accentuate VEGF secretion resulting in increased breakdown of the blood retinal barrier (BRB) and consequent DME deterioration.[15, 16] Therefore, the association of SCT with visual and anatomical outcomes should be elucidated.

In this study, we investigated the effects of IVZ on SCT as well as on central macular thickness (CMT) and on best corrected visual acuity (BCVA) changes in eyes with center-involved diabetic macular edema (CI-DME). A possible correlation between SCT changes and visual and anatomical outcomes of DME cases treated with IVZ is questioned.

METHODS

In this prospective interventional case series, cases of CI-DME were enrolled for intravitreal pharmacotherapy at Labbafinejad Medical Center, Tehran, Iran between April 2019 and April 2020.

The study protocol was reviewed and approved by the Ethics committee, Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, and the approval number was IR.SBMU.ORC.REC.1394.05. In addition, the protocol of the study complied with the guidelines for human studies and the tenets of Declaration of Helsinki. Informed consent was obtained from all participants.

Based on the standard protocols, all patients underwent three monthly IVZ injections (1.25 mg/0.05 ml).[17] Complete ocular examinations, Spectralis EDI-OCT (Heidelberg Engineering, Heidelberg, Germany), and SD OCT were performed at baseline and repeated one month after each IVZ injection. All visits and imaging procedures took place between 9 am and 12 am. BCVA was evaluated using the Snellen chart. CMT was assessed based on previously described OCT software methodology (the 1-mm Early Treatment Diabetic Retinopathy Study (ETDRS) circle centered on the fovea).[18] SCT was measured manually as the distance between the RPE hyperreflective line and the chorio-scleral junction. Only patients with CMTs of >250 μm and BCVA readings between 20/40 and 20/320 were included. Patients with proliferative diabetic retinopathy (PDR), concomitant macular disease, a history of intravitreal injections of anti-VEGFs or corticosteroids or retinal photocoagulation within three months of enrollment, a history of pars plana vitrectomy, refractive errors higher than ±5 diopters, a history of cardiovascular accidents, glaucoma, pregnancy, and uncontrolled systemic hypertension were excluded.

Statistical Analysis

Data were presented using mean, standard deviation, median and range, frequency, and percentage. Paired *T*-test was used to assess the improvement within the groups and *T*-test was used to evaluate the difference among the groups.

Minimal sample size needed for all variables was calculated as ≥45 individuals (G*Power software [latest ver. 3.1.9.7; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany]) to achieve a certain power (effect size dz = 0.5; α error probability = 0.05; power [1-β error probability] = 0.95). We also used generalized estimating equations (GEE) to consider the possible

correlation of the results in the eyes. Correlation of variables was assessed using Pearson's correlation coefficient. All statistical analyses were performed using the SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). *P*-value < 0.05 was considered statistically significant.

RESULTS

Fifty-seven eyes of 36 patients with CI-DME were included in this prospective interventional case series. During the study period, no patient missed follow-up sessions or required further treatments (e.g., laser photocoagulation, vitrectomy) and no complications related to IVZ were recorded in patients (signs of intraocular inflammation, change in the lens status, and systemic complications). Past medical history and ocular examination findings were summarized in Table 1.

CMT decreased progressively through IVZ monthly injections. A marginally significant decrease was recorded at the one month follow-up (P = 0.057); however, compared to the baseline a significant decrease was recorded after the second and third months. Progressive BCVA improvement was also observed after monthly IVZ injections. Significant changes were recorded after the second and third months as compared to the baseline. No significant changes in SCT were observed after monthly IVZ injections as compared to baseline [Table 2].

At each follow-up interval, the level of improvement of BCVA was correlated with the amount of CMT reduction. However, SCT did not correlate with changes in BCVA and CMT at follow-up visits [Table 3].

DISCUSSION

Ziv-aflibercept (Zaltrap) is a monoclonal antibody approved for the treatment of metastatic colorectal cancer. Like its analogue, aflibercept, Ziv-aflibercept blocks all isoforms of VEGF A, B, and placental growth factor (PlGF). While Ziv-aflibercept (Zaltrap) has higher osmolarity than aflibercept, studies showed no difference between the two drugs in the safety profile. Malick et al compared the toxicity of aflibercept, Ziv-aflibercept, bevacizumab, and ranibizumab on RPE cells in media culture. They observed mild mitochondrial toxicity following bevacizumab and ziv-aflibercept injections.[19] In an experimental study, 0.05 ml IVZ had no deleterious effect on the osmolarity of the vitreous.[20] Mansour et al showed the effect of IVZ in patients with DME without any intraocular toxicity.[9] Chhablani et al demonstrated the effect of IVZ injection on patients with neovascular AMD with no intraocular toxicity or retinal electrophysiological abnormalities.[21] Additionally, no significant adverse effects related to IVZ were detected, at least in a short-term follow-up. However, long-term adverse effects of IVZ remains unknown.

Variable results have been reported regarding choroidal thickness changes in patients with DME.[14, 15, 22] There are reports of reduced choroidal thickness in these patients, which may be the consequence of choroidal vascular obstruction and development of non-perfusion areas similar to retinal vascular alterations.[15, 22] A histopathological study revealed thinning and attenuation of the choriocapillaris layer with subsequent reduction of choroidal thickness in diabetic retinopathy.[14] Meanwhile, some studies showed increase of choroidal thickness in patients with DME. VEGF overexpression causes dilation and congestion of choroidal vessels that result in thicker choroid in patients with DME. Therefore, anti-VEGFs for DME treatment could theoretically reduce the permeability and thickness of choroidal layers. However, no significant association was found between anti-VEGF therapy and choroidal thickness changes in patients with CI-DME.

The effect of anti-VEGF treatment on choroidal thickness in DME has already been evaluated.[3, 12–14, 23–25] Several studies reported reduction of choroidal thickness following intravitreal injection of bevacizumab (IVB).[3, 12, 23] Rayess et al revealed that thicker baseline SCT was associated with better anatomic and functional responses. They suggested baseline SCT as a predictor of DME treatment response to IVB.[12] Yiu et al reported no correlation between SCT reduction and changes in visual acuity (VA) and macular thickness.[3] In a clinical trial, no significant changes were observed in choroidal thickness following IVB injection in DME.[24] Recently, it has been shown that intravitreal aflibercept had more effect on SCT in DME as compared to intravitreal ranibizumab.[25]

Despite previous investigations using various forms of anti-VEGFs, the effect of IVZ on choroidal

Table 1. Baseline characteristics and demographic features.

		N (%)
Eye	OD	30 (52.6%)
	OS	27 (47.4%)
Lens status	Pseudophakic	20 (35.1%)
	Phakic	37 (64.9%)
History of MPC	No	31 (54.4%)
	Yes	26 (45.6%)
History of injection	No	28 (49.1%)
	Yes	29 (50.9%)
Naïve	No	36 (63.2%)
	Yes	21 (36.8%)
Age	Mean ± SD	63.3 ± 5.93
Number of injection	Mean ± SD	3.93 ± 1.03
Duration of diabetes (yr)	Mean ± SD	12.37 ± 4.23

MPC, macular photocoagulation; OD, right eye; OS, left eye; SD, standard deviation

Table 2. Best-corrected visual acuity, central macular thickness, subfoveal choroidal thickness before and at one, two, and three months after monthly injection of intravitreal ziv-aflibercept.

	Baseline	Month 1			Month 2			Month 3		
	Values	Values	Changes	P-value	Values	Changes	P-value	Values	Changes	P-value
BCVA	0.58 ± 0.29	0.47 ± 0.31	−0.15 ± 0.22	0.202	0.4 ± 0.24	−0.19 ± 0.26	0.002	0.37 ± 0.23	−0.22 ± 0.27	<0.001
CMT	396 ± 119	344 ± 115	−52 ± 123	0.057	305 ± 89	−91 ± 132	<0.001	296 ± 101	−102 ± 144	<0.001
SFCT	236 ± 47	245 ± 56	9 ± 55	>0.99	254 ± 54	18 ± 55	0.197	241 ± 54	7 ± 61	>0.99

P-value calculated using paired *T*-test
BCVA, best-corrected visual acuity; CMT, central macular thickness; SFCT, subfoveal choroidal thickness

Table 3. Correlation between central macular thickness changes, best corrected visual acuity changes, and subfoveal choroidal thickness changes at one, two, and three months after monthly injection of intravitreal ziv-aflibercept.

Time		CMT and BCVA	SFCT and CMT	SFCT and BCVA
Month 1	Pearson Correlation	0.436**	0.186	−0.025
	P-value	0.002	0.165	0.864
Month 2	Pearson Correlation	0.446**	0.006	0.028
	P-value	0.001	0.966	0.845
Month 3	Pearson Correlation	0.456**	0.104	0.047
	P-value	0.001	0.453	0.743

**Correlation is significant at the 0.01 level (2-tailed)
BCVA, best-corrected visual acuity; CMT, central macular thickness; SFCT, subfoveal choroidal thickness

thickness in DME has not been evaluated so far. In our study, SCT did not significantly change after IVZ injection in patients with CI-DME. In addition, despite adequate sample size and statistical power of the analysis, we observed no correlation between SCT and changes of CMT and BCVA after IVZ injections. It might be related to different receptor density and sensitivity of retinal and choroidal vasculature to VEGF. It is believed that choroidal thickness reduction in DME may be related to factors other than VEGF. Hence, VEGF may not be the sole contributor to choroidal thickness changes in DR.[26]

There were few limitations in the current study. It lacked a contralateral eye comparison. The absence of correlation between IVZ and changes in choroidal thickness might be related to the short follow-up time of the study. In addition, we did not compare the effect of IVZ with other forms of anti-VEGFs. SCT changes might not represent the changes of the entire choroidal tissue. A more detailed assessment of the choroidal vascular index and stromal area could be a better way to assess the choroidal structure changes in response to intravitreal anti-VEGF injections.

In summary, IVZ is a promising form of anti-VEGF drug used to improve visual and anatomical outcomes in patients with CI-DME without significant short-term toxicity. The visual and anatomical effects of IVZ on DME are not correlated with any changes in SCT.

Financial Support and Sponsorship

None.

Conflicts of Interest

None of the authors have any conflicts of interest to declare.

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Original Article

Renal Function following Fluorescein Angiography in Diabetic Patients with Chronic Kidney Disease

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Abstract

Purpose: To evaluate the effect of fluorescein dye usage on renal function in patients with diabetic retinopathy (DR) and chronic kidney disease (CKD).
Methods: Diabetic patients with retinopathy who were candidate for fundus fluorescein angiography (FA) were evaluated for serum creatinine and urea levels within five days prior to performing the FA. Serum creatinine levels of 1.5 mg/dl or more in males and 1.4 mg/dl or more in females were both identified as CKD and were included in the study. An increase of 0.5 mg/dl or 25% in creatinine after FA was considered as contrast-induced acute kidney injury (AKI). Estimated glomerular filtration rate (eGFR) was also calculated for all patients using a CKD-Epi formula. CKD grading was determined based on eGFR values.
Results: Forty-two patients agreed to participate, of which 23 (54.8%) were male. Seventeen patients were identified with grade 3a or lower CKD, 12 with grade 3b, 11 with grade 4, and two with grade 5 CKD. Considering all grades of CKD, the mean blood urea before and after angiography was 58.48 ± 26.7 and 57 ± 27.81 mg/dl, respectively (P = 0.475). The mean serum creatinine before and after the test was 1.89 ± 1.04 and 1.87±0.99 mg/dl, respectively (P = 0.993). The mean eGFR before and after the test was 44.024 ± 23.5447 and 43.850 ± 21.8581 mL/min/1.73 m^2 (P = 0.875).
Conclusion: According to the findings of this study, FA does not seem to further deteriorate kidney function in patients with diabetic associated CKD.

Keywords: Acute Kidney Injury; Chronic Kidney Disease; Diabetic Retinopathy; Fluorescein Angiography; Nephropathy; Serum Creatinine

J Ophthalmic Vis Res 2023; 18 (2): 170–174

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Received: 19-02-2022 Accepted: 10-12-2022

Access this article online

Website: https://knepublishing.com/index.php/JOVR

DOI: 10.18502/jovr.v18i2.13183

How to cite this article: Ebrahimiadib N, Mirzaei SH, Riazi-Esfahani H, Amini M. Renal Function following Fluorescein Angiography in Diabetic Patients with Chronic Kidney Disease . J Ophthalmic Vis Res 2023;18:170–174.

INTRODUCTION

Fundus fluorescein angiography (FA) is a valuable method to evaluate microvascular complications in patients with diabetic retinopathy (DR). This procedure involves injection of fluorescein dye, which is a non-ionizing contrast, intravenously. Fluorescein dye is metabolized by the kidneys and excreted in the urine during the first 48–72 hr after injection.[1] During this time, contrast-induced nephropathy usually manifests.[2]

Considering that concomitant diabetic nephropathy is possible in patients with DR, there is a concern as to whether fluorescein usage can deteriorate the kidney function further.[1–4] Chronic kidney disease (CKD) is defined as a gradual decline in renal function which is initially subclinical. Contrast-induced acute kidney injury (AKI) is defined by an increase in serum creatinine of ≥0.5 mg/dl or 25% from the baseline that occurs around 48 hr after contrast administration.[1]

Although renal side effects have been attributed to fluorescein usage in previous studies, there is still no consensus in this regard.[5, 6]Some angiography centers require a nephrology consult, in addition to blood and urine workup, before preceding to FA in patients with CKD. Apart from the burden of cost and time on patients and healthcare system, referral of these patients for additional testing may cause a delay in diagnosis and treatment of the eye condition.

In this study, we are going to determine whether the fluorescein can cause contrast-induced AKI in diabetic patients with CKD who are candidates for fundus FA.

METHODS

This prospective study was performed in the retinal imaging section of Farabi Eye Hospital from January 2019 until January 2020. The study protocol was reviewed and approved by the ethics committee of Tehran University of Medical Sciences under approval number 96014334034. Prior to recruitment, all patients were informed of the details of the study through verbal and written communication. According to the Helsinki Declaration, a written consent was also obtained from patients.

Patients with DR who were referred to the imaging section for performing FA to confirm the stage of retinopathy were routinely asked for a history of renal dysfunction. Those with a positive history were sent for blood test to determine urea and creatinine levels. If creatinine levels were ≥1.5 mg/dl in men and ≥1.4 mg/dl in women, they were included in the study.[7]The glomerular filtration rate (GFR) (ml/min/1.73 m^2) was calculated for all patients based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[8]The CKD grading was determined based on the eGFR levels. According to the Kidney Disease Outcomes Quality Initiative guidelines, eGFR of ≥90 ml/min per 1.73$m^2$is considered stage 1 CKD, 60–89 stage 2, 30–59 stage 3 (45–59 stage 3a and 30–44 stage 3b), 15–29 stage 4, and <15 would be considered stage 5 CKD.[8]

The process of FA involved an injection of 2.5 ml of 10% fluorescein sodium solution (1g/5cc) [Sterop, Belgica] into the antecubital vein access in 5 s. For at least 10 min after the dye injection, fundus images were captured by Heidelberg retina angiography with confocal SLO (Heidelberg Engineering, Heidelberg, Germany). Patients were then monitored for about 15 more minutes for any complications. Blood urea and creatinine levels were retested 48–72 hr after the fluorescein injection. Serum creatinine levels, before and after contrast administration, were compared and if increased by ≥0.5 mg/dl or 25% from the baseline were considered as AKI.[2]

Moreover, patients who had received contrast material for imaging during the prior two months or those with kidney failure due to another cause, final stage of renal dysfunction requiring dialysis, chronic heart failure, pregnancy and breastfeeding, history of sensitivity to the contrast agent, consumption of nonsteroidal anti-inflammatory drug, angiotensin receptor blocker, angiotensin converting enzyme inhibitor, or intravenous diuretic were all excluded from the study.

Data analysis was performed using the SPSS software version 18 (SPSS, Inc., Chicago, IL, USA). Alterations of the variables with normal distribution was analyzed using paired sample *t*-test, and Wilcoxon singed-rank test was used to compare nonparametric variables. $P < 0.05$ was considered as significant.

RESULTS

We included 42 patients, with the mean age of 58.1 years. Of them, 23 (54.8%) were male. Regarding

the CKD grading, 17 patients were identified with grade 3a or lower CKD, 12 with grade 3b, 11 with grade 4, and two with grade 5.

Overall mean urea in patients before and after angiography was 58.48 ± 26.7 and 57 ± 27.81 mg/dl, respectively (P = 0.475).

The mean serum creatinine levels were 1.89 ± 1.04 and 1.87± 0.99 mg/dL as the pre- and post-angiography values (P = 0.993). The mean eGFR before and after the test was 44.024 ± 23.5447 and 43.850 ± 21.8581 mL/min/1.73 m^2 (P = 0.875) [Table 1].

Differential changes in eGFR before and after FA in all stages of CKD was not significant [Table 2].

Discussion

Findings in our study showed that FA does not exacerbate kidney dysfunction (AKI) in diabetic patients with an already reduced GFR (CKD). Therefore, for patients with diabetic nephropathy in this instance who are candidates for FA, nephrology consult or additional tests before and after fluorescein injection are not required.

In a retrospective study by Kameda et al, patients' serum creatinine level within one month before and after FA were investigated to calculate the estimated glomerular filtration rate (eGFR). They categorized patients with eGFR of <60 ml/min/m^2 into three grades of severity from grade 3 to 5 CKD. None of these subgroups showed a significant alteration in eGFR following fluorescein injection.[3]

In another study by Chung et al, patients were divided into three categories based on serum creatinine levels before angiography; including low (<1.5 mg / dl), moderate (1.5–2 mg/dl), and high (>2 mg/dl).[9]Then, the effect of FA on renal function was evaluated in these patients. However, the actual timing that they tested the serum creatinine levels before and after FA was indeterminate, especially as there were some delayed measurements after FA, which might have influenced the omission of cases with AKI. AKI definitions are based on changes up to a maximum of seven days following the presumed insult.[10]They also included patients with other causes of renal dysfunction other than diabetes. They reported a significant change in serum creatinine levels in the high-risk group and suggested caution be applied for these patients.[9]

In another study by Alemzadeh et al on 44 diabetic patients, serum creatinine levels showed a significant increase 72 hr after FA in 20% of patients. In contrast to studies by Kameda and Chung, Alemzadeh study showed that an increase in serum creatinine and AKI can happen secondary to FA. However, their patients were not categorized in terms of kidney damage.[11] In our study, although the mean creatinine level was higher as compared to the Alemzadeh's study both before and after FA, the dose of injected fluorescein was 250 mg which was half of the dose used in their study.

Kidney damage and increase in serum creatinine following the use of contrasts in susceptible patients has been attributed to vasoconstriction, which reduces blood flow to the medulla. Of note, renal blood flow auto regulation is defective in patients with CKD. Identifying high-risk patients and preventing the occurrence of AKI is critical,[12]especially as diabetes mellitus is the leading cause of propensity toward renal dysfunction.

It is noteworthy that most kidney damage related to contrast agents has been due to iodinated contrast agents, while fluorescein is a non-iodinated one.[13–16] However, in a recently published article with a retrospective design, fluorescein was found to play a role in the progression of nephropathy. Nevertheless, the authors were not sure of the clinical significance of their result due to two reasons. Firstly, under normal circumstances fluctuations of up to 15% are possible each time the serum creatinine level is tested. The second reason is related to the criteria used; in a patient with AKI, creatinine-based formulas are prone to overestimating the eGFR. Therefore, due to uncertainty about creatinine levels, their conclusion about the effect of the fluorescein on nephropathy is dubious.[17]

Our study was a prospective study on patients with DR and CKD. We found no significant effect on renal function shortly after performing FA. We used half of the recommended dosage of fluorescein and could still obtain good-quality images of fundus angiography. Nephrology consults and further evaluation for these group of patients seem to be unnecessary.

There are two major limitations for our study. Firstly, the relatively small number of cases. Secondly, we did not categorize our patients according to the multiple types of medications

Table 1. Values of blood urea and creatinine levels and estimated GFR, before and after fluorescein angiography in patients with chronic kidney disease.

Grades of CKD	eGFR (mL/min/1.73 m^2)		P-value
	Pre	Post	
G1	98.50 ± 3.50	89.70 ± 11.05	0.309
G2	67.13 ± 7.98	64.20 ± 7.86	0.430
G3a	50.62 ± 5.12	51.25 ± 10.38	0.822
G3b	37.65 ± 5.44	40.54 ± 8.03	0.133
G4	21.74 ± 4.52	22.18 ± 4.23	0.640
G5	10.95 ± 5.02	10.50 ± 4.10	0.614

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

Table 2. Alteration of eGFR following fluorescein angiography.

		Mean ± SD (range)	Median (range)	95% CI		P-value
				Lower	Upper	
Urea (mg/dL)	Pre	58.48 ± 26.7 (0.7–6)	55 (23 to 134)			
	Post	57 ± 27.81	46 (21 to 126)			
	Change	–1.48 ± 13.27	1.5 (–35 to 25)	–5.61	2.66	0.475
Creatinine (mg/dL)	Pre	1.89 ± 1.04 (0.7–6)	1.65 (0.7 to 6)			
	Post	1.87 ± 0.99 (0.7–5.9)	1.55 (0.7 to 5.9)			
	Change	–0.02 ± 0.25	0 (–1.1 to 0.4)	–0.1	0.06	0.993
eGFR by CKD-Epi (mL/min/1.73 m^2)	Pre	44.024 ± 23.54 (7.4–102)	55 (7 to 98)			
	Post	43.850 ± 21.86 (7.6–97.1)	46 (7 to 95)			
	Change	–0.174 ± 22.69	0.17 (–40 to 67)	–2.039	2.38	0.875

SD, standard deviation; CI, confidence interval; CKD-Epi, chronic kidney disease epidemiology collaboration equation; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

used by each patient; such as oral hypoglycemic agents, diuretics, or statins. However, as overall we did not observe fluorescein injection causing any AKI, lack of such data might not be affecting the results.

Financial Support and Sponsorship

None.

Conflicts of Interest

None.

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Original Article

P100 Wave Latency and Amplitude in Visual Evoked Potential Records in Different Visual Quadrants of Normal Individuals

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Abstract

Purpose: Assessment of the pattern visual evoked potential (PVEP) responses in different areas of visual fields in individuals with normal vision.
Methods: This study was conducted on 80 eyes of normal subjects aged 18–35 years. All participants underwent refraction and visual acuity examination. Visual evoked potential (VEP) responses were recorded in different areas of field. The repeated measure test was used to compare the P100 latency and amplitude of PVEP among different areas.
Results: The repeated measures analysis of variance showed a statistically significant difference among different areas in terms of amplitude and latency of P100 ($P = 0.002$ and $P < 0.001$, respectively). According to the results, the highest and lowest amplitude of P100 was observed in inferior-nasal and superior areas, respectively. The highest and lowest latency of P100 was related to the temporal and inferior-nasal areas, respectively.
Conclusion: This study partially revealed the details of local PVEP distribution in the visual field and there was a significant difference in the amplitude and latency of PVEP wave in different areas of the visual field.

Keywords: Amplitude; Latency; Normal Vision; Pattern Reversal; Visual Evoked Potential; Visual Field

J Ophthalmic Vis Res 2023; 18 (2): 175–181

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Received: 06-01-2022 Accepted: 05-12-2022

Access this article online

Website: https://knepublishing.com/index.php/JOVR

DOI: 10.18502/jovr.v18i2.13184

How to cite this article: Mirzaee Saba L, Hashemi H, Jafarzadehpour E, Mirzajani A, Yekta A, Jafarzadehpour A, Zarei A, Nabovati P, Khabazkhoob M. P100 Wave Latency and Amplitude in Visual Evoked Potential Records in Different Visual Quadrants of Normal Individuals . J Ophthalmic Vis Res 2023;18:175–181.

INTRODUCTION

Visual field (VF) plays a significant role in clinical optometry and assessment of VF findings is important in the diagnosis and treatment of the diseases like glaucoma.[1,2] Humphrey perimetry is the gold standard for detection of visual field defects; however, it has some limitations.[3] As it is a subjective test, it is largely patient dependent and the test duration may vary depending on the aptitude of the examinee. Many individuals, especially older patients, are weak on subjective tests.[4–6] Subjective perimetry is associated with a learning curve leading to complicating interpretation of the results in new patients. As a result, the test should be performed two to three times to obtain a valid result.[3,7] Moreover, it is expected that a considerable loss of ganglion cells occurs before standard perimetry shows a visual field defect. Therefore, more sensitive tests are required because about 25–50% of optic nerve fibers may be lost before a visual field defect is actually diagnosed.[4, 8]

Electroretinogram (ERG)[7] and visual evoked potential (VEP) are two objective methods used for the measurement of visual field sensitivity.[3, 8] Studies show that multifocal visual evoked potential (mfVEP) is one of the most advanced technology used in the measurement of visual field sensitivity.[9] Stability of the mfVEP system depends on a number of environmental factors. Since the VEP amplitude is measured within the range of microvolts, environmental factors such as noises that result from problems which occur with cortical electric changes in power supply such as voltage fluctuations may cause amplitude changes in one area of the field when presenting the stimulus. Therefore, in order to decrease the noise effect, the calculation of more comparative averages is required for an overall more accurate averaging assessment. Unfortunately, the technology used in the mfVEP software does not produce many averages because the examination is time consuming.[3, 10] In addition, as the mfVEP software is very complicated and costly, most centers are not equipped with the software. The present study aimed to assess the sensitivity of pattern visual evoked potential (PVEP) in different areas of visual field while considering the need for objective perimetry with the unavailability of the mfVEP software, and also considering the emphasis on clinical electrophysiology standards regarding multiple definitions of "normal" for age and race.[10] To decrease the effect of noise, the averaging of 100 measurements was considered in each area. For this purpose, a stimulus was presented at each of the eight areas to measure P100 amplitude and latency in PVEP records of visually normal participants.

METHODS

This cross-sectional study was conducted to assess the P100 amplitude and latency of PVEP in different visual field areas in visually normal individuals in the Ophthalmic Electrophysiology Clinic of the School of Rehabilitation, Iran University of Medical Sciences. The participants were selected from eligible individuals attending the clinic who were willing to join the study and signed an informed consent form through convenient sampling. The inclusion criteria were as follows: (1) age 18–35 years, (2) corrected distance visual acuity of 20/20 or better in both eyes (best visual acuity 20/20 with or without correction), (3) myopia <–3 diopters (D) or astigmatism <2D,[11] and (4) lack of any systemic diseases that might affect PVEP results.

Based on the values obtained from the articles, the mentioned standard deviation reported to be around 4.7.[12] Taking into account the value of d equal to 2 and the confidence level of 95% and z equal to 1.96, based on the following equation the calculated number of samples would be 21; we however examined 40 people in this study.

$$N = \frac{Z^2\delta^2}{d^2}.$$

The objective of the study was explained to the participants. First, visual acuity was tested with a Snellen chart and then objective refraction was measured using a Heine retinoscope (Heine, Germany) and the Huvitz HRK-8000 autorefractometer (Huvitz, South Korea). Subjective refraction responses were also evaluated. Eyes were examined with slit lamp and ophthalmoscope for eye pathology determination. In the next stage, the P100 amplitude and latency of PVEP were recorded in mesopic conditions.

PVEP

The P100 amplitude and latency of PVEP was assessed and recorded by Metro Vision (Mon pack

3, Perenchies, France) with a check size of 30 min of arc with a contrast of 85%. The test was performed monocularly under mesopic conditions (low-light conditions that are not completely dark) since it is more similar to everyday natural viewing conditions. In this study, the P100 latency and amplitude of the PVEP were measured using passive, active, and ground electrodes. The placement of PVEP electrodes was based on the International 10/20 system.[12] Before the test was conducted, in an effort to achieve better signal transmission, the skin's dead layers were removed with alcohol. The electrodes, which were filled with conductive gel, were then placed on appropriate places on the head and forehead using a special adhesive paste. The resistance of the electrode/skin junction was <5K Ohms. After recording the patient's name, the patient sat at a distance of 1 m from the stimulation display and the test was performed monocularly. First, a full-field PVEP was recorded for each patient; then, as the patient looked at the fixation point in the middle of the screen, a stimulus was randomly presented at different locations of the screen and the P100 amplitude and latency of PVEP was recorded in the superior-nasal, inferior-nasal, superior-temporal, and inferior-temporal areas as well the superior, inferior, nasal, and temporal areas of the visual field. Each of the visual field areas in the periphery were 30° away from the center. An example of a visual field area is shown in the Figure 1.

The SPSS version 20 was used for statistical analysis. Mean and standard deviation were used to describe the data. According to the Kolmogorov–Smirnov test, all components had a normal distribution. Since the data of different areas within the visual field in each eye was interdependent, repeated measures analysis of variance was used to compare them. A post hoc least significant difference (LSD) test was performed to show comparisons. In this study, a significance level of 0.05 was considered.

Considering that both eyes were analyzed, the correlation effect of fellow eyes was controlled in the analysis.

Ethical Considerations

The Ethics Committee of Iran University of Medical Sciences approved the study protocol by the registration number of IR.IUMS. FMN.1395.02, which was conducted in accordance with the tenets of the Helsinki Declaration. All participants signed a written informed consent.

RESULTS

In this study, the mean P100 amplitude and latency were assessed in different visual field areas of 80 eyes of 40 patients with a mean age of 23.25 ± 3.44 years.

Of the 40 studied individuals, 20 were women. Table 1 shows the mean and standard deviation of the P100 amplitude and latency in different areas of the visual field. There was no statistically significant difference in the average amplitude and latency of P100 in all areas between males and females ($P > 0.05$).

The repeated measures analysis of variance showed a statistically significant difference among the different areas in terms of amplitude and latency of P100 ($P = 0.002$ and $P < 0.001$, respectively). According to the results, the highest and lowest amplitude of P100 was observed in the inferior-nasal and superior areas, respectively. The highest and lowest latency of P100 was related to the temporal and inferior-nasal areas, respectively. Table 2 shows the comparison of the P100 amplitude and latency in the different areas of the visual field, and the effect size values are also presented. All comparisons were reported using Bonferroni post-hoc test with Bonferroni correction.

DISCUSSION

According to Tables 1 and 2, there were variances in the recorded latency and amplitude values among different areas within the visual field, which were sometimes significant. Therefore, it seems that within different areas of the retina with corresponding paths, and with the same neurons, the transmission speed of the messages was not the same, and did not have the same destination in the cortex. Some studies also suggest that these differences exist.[12, 13] As Silveira points out in her study, the conduction velocity of parvocellular (P) cells is slower than that of magnocellular (M) cells and about 80% of all ganglion cells are parvocellular cells.[14]

According to clinical findings and electrophysiological standards, P100 is the

Table 1. The mean and standard deviation (SD) of P100 amplitude and latency in different areas of visual field.

	Latency of P100 (ms)	Amplitude of P100 (microV)
Areas	**Mean ± SD**	**Mean ± SD**
Full	103.99 ± 6.63	7.95 ± 3.9
Nasal	103.57 ± 12.37	3.89 ± 1.99
Temporal	101.4 ± 7.28	5.19 ± 2.25
Superior	100.22 ± 8.16	4.85 ± 2.82
Inferior	102.48 ± 10.46	3.5 ± 1.76
Superior nasal	100.17 ± 12.95	3.24 ± 1.89
Inferior nasal	109.07 ± 14.52	2.76 ± 1.61
Superior temporal	100.92 ± 8.39	3.9 ± 1.67
Inferior temporal	98.85 ± 8.12	3.22 ± 1.51

SD, standard deviation; ms, millisecond, microV, microvolts

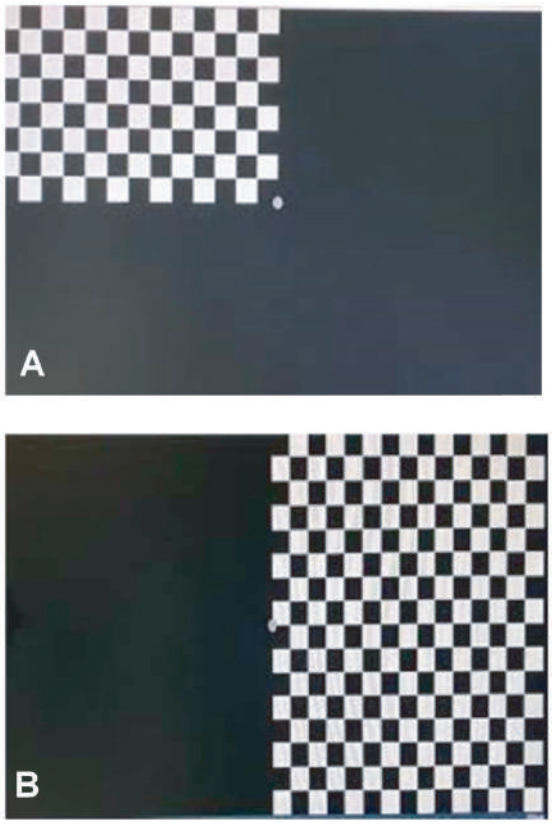

Figure 1. Area pattern (A) and hemifield (B) patterns of visual evoked potential used in this study.

most important and stable component of the PVEP.[12, 14] Table 1 presents an assessment of P100 latency and amplitude. Considering the importance of P100 latency of PVEP,[12] Table 1 delineates the most important index for the assessment of recorded results. According to Table 1, neurons in the inferior temporal area are the fastest and/or most superficial and/or the closest neurons to active PVEP electrodes. According to studies by Baseler et al, the central

Table 2. Comparison of P100 amplitude and latency in different areas of visual field.

		Amplitude of P100 (microV)		Latency of P100 (ms)	
	Quadrans	Effect size (95%CI)	P-value*	Effect size (95%CI)	P-value*
Full	Nasal	4.06 (2.91–5.22)	<0.001	0.42 (-3.27–4.11)	1.000
	Temporal	2.76 (1.58–3.94)	<0.001	2.59 (-0.06–5.25)	0.063
	Superior	3.10 (2.15–4.05)	<0.001	3.77 (1.26–6.28)	<0.001
	Inferior	4.45 (3.16–5.73)	<0.001	1.51 (-1.73–4.74)	1.000
	Superior nasal	4.71 (3.39–6.03)	<0.001	3.82 (-0.55–8.19)	0.177
	Inferior nasal	5.19 (3.68–6.69)	<0.001	-5.08 (-10.9–0.75)	0.179
	Superior temporal	4.05 (2.82–5.28)	<0.001	3.07 (0.02–6.12)	0.047
	Inferior temporal	4.73 (3.31–6.15)	<0.001	5.14 (2.55–7.72)	<0.001
Nasal	Temporal	-1.31 (-2.22–0.39)	<0.001	2.17 (-2.35–6.7)	1.000
	Superior	-0.97 (-1.82–0.11)	0.012	3.35 (-0.40–7.10)	0.145
	Inferior	0.38 (-0.48–1.25)	1.000	1.09 (-4.06–6.24)	1.000
	Superior nasal	0.64 (-0.06–1.35)	0.119	3.4 (-0.78–7.58)	0.306
	Inferior nasal	1.12 (0.22–2.02)	0.003	-5.5 (-12.23–1.23)	0.300
	Superior temporal	-0.01 (-0.81–0.79)	1.000	2.65(-1.94 -7.24)	1.000
	Inferior temporal	0.67 (-0.14–1.47)	0.273	4.72 (0.58–8.86)	0.011
Temporal	Superior	0.34 (-0.6–1.28)	1.000	1.18 (-1.96–4.31)	1.000
	Inferior	1.69 (0.82–2.56)	<0.001	-1.08 (-4.56–2.39)	1.000
	Superior nasal	1.95 (0.94–2.95)	<0.001	1.23 (-3.40–5.86)	1.000
	Inferior nasal	2.43 (1.41–3.44)	<0.001	-7.67 (-14.14–1.2)	0.007
	Superior temporal	1.29 (0.59–2.00)	<0.001	0.48 (-1.87–2.82)	1.000
	Inferior temporal	1.97 (1.08–2.86)	<0.001	2.55 (-0.80–5.89)	0.491
Superior	Inferior	1.35 (0.33–2.37)	<0.001	-2.26 (-6.15–1.63)	1.000
	Superior nasal	1.61 (0.60–2.61)	<0.001	0.05 (-3.72–3.82)	1.000
	Inferior nasal	2.09 (0.91–3.27)	<0.001	-8.85 (-14.98–2.72)	0.000
	Superior temporal	0.95 (-0.04–1.94)	0.075	-0.7 (-4.31–2.91)	1.000
	Inferior temporal	1.63 (0.55–2.71)	0.000	1.37 (-2.04–4.78)	1.000
Inferior	Superior nasal	0.26 (-0.60–1.12)	1.000	2.31 (-2.59–7.22)	1.000
	Inferior nasal	0.74 (-0.15–1.63)	0.250	-6.59 (-13.10–0.08)	0.044
	Superior temporal	-0.4 (-1.18–0.39)	1.000	1.56 (-2.09–5.21)	1.000
	Inferior temporal	0.28 (-0.45–1.01)	1.000	3.63 (0.17–7.08)	0.029
Superior nasal	Inferior nasal	0.48 (-0.37–1.33)	1.000	-8.9 (-16.05–1.75)	0.003
	Superior temporal	-0.66 (-1.46–0.15)	0.307	-0.75 (-5.61–4.11)	1.000
	Inferior temporal	0.02 (-0.75–0.79)	1.000	1.32 (-3.26–5.89)	1.000
Inferior nasal	Superior temporal	-1.14 (-1.9–0.37)	<0.001	8.15 (1.25–15.05)	0.007
	Inferior temporal	-0.46 (-1.12–0.20)	0.892	10.22 (4.10–16.33)	<0.001
Superior temporal	Inferior temporal	0.68 (-0.03–1.39)	0.082	2.07 (-1.51–5.65)	1.000

*Adjustment for multiple comparisons: Bonferroni
CI, confidence interval; ms, millisecond, microV, microvolts

visual field which is mainly composed of P cells, sends stimuli to the inferior temporal area of the cortex, and the peripheral visual field, which is mainly caused by M cells, sends stimuli to the posterior area of the parietal cortex.[15, 16] According to Horton's findings, macular fibers are generally located in the posterior area of the occipital lobe close to the electrode site, while as we move toward the periphery, the fibers are present in the anterior area of the cortex.[16, 17] In addition, according to Holliday and Michael, producers of PVEP responses in the cortex are located at different distances from the active electrode.[18] Also, according to studies performed with functional magnetic resonance imaging (fMRI), fovea is presented in the posterior occipital region and areas with increased eccentricity in the anterior area. The peripheral field is at the back of the parietal cortex and near the junction of the calcarine fissure. The horizontal meridians of the field are in the range of the calcarine fissure and the presentation of the upper part of the vertical meridians is below the calcarine fissure.[16]

The findings of the recorded amplitude indicate the difference in neuronal density,[19] change distance recorded,[20] and inhibitory response.[21] According to Table 1, the amplitude corresponding to the inferior temporal area findings was not among high recorded amplitudes.

The reason could be that the density of P and M ganglion cells decreases toward the periphery.[22, 23] On the other hand, the recording interval is also effective in the responses. In humans, the visual cortex is projected along the superior and inferior regions of the calcarine fissure. The upper region of the calcarine fissure corresponds to the upper region of the retina where the lower visual field is represented and the upper visual field is represented above the calcarine fissure. According to a study by Jeffroys et al, since the producers of the superior field are under the fissure and further away from the active electrode as compared to the producers of the inferior field, a lower amplitude is expected in the lower half of the retina,[11, 18] which is consistent with our findings.

After the inferior temporal area, the fastest or the most superficial response was related to the superior nasal area, followed by the superior and superior temporal areas. The ganglion cells of the superior area of the retina are projected to the superior and medial regions of the lateral geniculate body. These superior fibers are then projected to the posterior region of the parietal lobe[20] and are therefore relatively closer to the active electrode.

The amplitude corresponding to the superior and superior temporal areas was the highest amplitude recorded in the study. This finding may indicate a higher density of ganglion cells in the superior retina. On the other hand, these cells are located above the calcarine fissure and are closer to the active electrode as compared to the inferior area and therefore already possess better amplitude. The superior temporal area had higher amplitude than the superior nasal area. On average, above the horizontal meridian, the temporal retina had the larger response than the nasal retina.[11]

The temporal retina had the highest response amplitude, indicating the greater density of nerve fibers in this region.[16] The inferior and nasal retina regions of the retina have a lower amplitude and higher latency. The ganglion cells of the inferior retina are projected to the temporal region of the lateral geniculate body. The ganglion cells of the nasal retina are projected to the contralateral lateral geniculate body in layers 1, 4, and 6; therefore, they are farther away from the ipsilateral active electrode and far from contralateral electrode.[20]

On the other hand, in the retinal periphery, the density of ganglion cells is higher in the nasal area, producing a better amplitude than the inferior area.[22] The ganglion cells of the center are more superficial while the ganglion cells of the periphery are deeper.[24] The neurons become deeper and their latency increase as we move from the fovea toward the periphery. Moreover, the inferior nasal had the lowest amplitude in the study. These fibers are projected to the contralateral geniculate body and are farther away from the active electrode.[20] Similar to our study, Min ZHONG's study investigated the topographical changes of the visual field with VEP, which, of course, examined the parameters of the VEP wave in 37 areas of the visual field, with a matrix stimuli including a 61 hexagons pattern. In his study, latency is reduced in the temporal region.[11]

Based on the conducted studies, factors such as the position of the electrodes, neuronal density and pathway, and the size of the stimulus affect the electrophysiological responses. Since the majority of the striate cortex responses is related to the

central visual field which is presented at the tip of the occipital poles which is closer to the active electrode, a decrease in the responses was seen from the center to the periphery considering the cellular density, distribution of magnocellular and parvocellular neurons, and differences in the velocity of conducting messages to the cortex.

The suggestion for further research is to perform these assessments in patients with glaucoma and other conditions associated with visual field defects and compare the findings with standard perimetry results to determine whether early diagnosis would be possible.

A major limitation of this study is the lack of eye tracking during the PVEP test, hence the possibility of fixation instability and unwanted fine eye movements during the test could affect the accuracy of the results.

In summary, this study evaluated the details of local PVEP distribution in different areas of the visual field. Considering the significant difference in the amplitude and latency of the PVEP in different areas, the inferior temporal (lowest latency) and temporal (highest amplitude) areas have the highest visual sensitivity. These findings are in line with the results of other studies.

Financial Support and Sponsorship

None.

Conflicts of Interest

No conflicting relationship exists for any author.

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Original Article

Rapid Assessment of Avoidable Visual Impairment in Two Coastal Districts of Eastern India for Determining Effective Coverage: A Cross-Sectional Study

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Abstract

Purpose: To measure the prevalence and causes of visual impairment (VI) among the 40+ age population in two coastal districts of India and to determine the levels of effective cataract surgical coverage (eCSC) and effective refractive error coverage (eREC) in the study population.

Methods: A cross-sectional study was done on 4200 people chosen using cluster sampling in two coastal districts of Odisha, an eastern state in India. A team consisting of trained optometrists and social workers conducted the ocular examination which included unaided, pinhole, and aided visual acuity assessments followed by examination of the anterior segment and lens.

Results: Overall, 3745 (89.2%) participants were examined from 60 study clusters, 30 in each district. Among those examined, 1677 (44.8%) were men, 2554 (68.2%) were educated and number? (17.8%) used distance spectacles during the survey. The prevalence of VI adjusted for age and gender was 12.77% (95% CI 11.85–13.69%). Multiple logistic regression showed that older age (OR 3.1; 95% CI 2.0–4.7) and urban residence (OR 1.2; 95% CI 1.0–1.6) were associated with VI. Being educated (OR 0.4; 95% CI 0.3–0.6) and using glasses (OR 0.3; 95% CI 0.5–0.2) were found to provide protection; therefore, resulting in lower instances of VI. Cataract (62.7%) and uncorrected refractive errors (27.1%) were the two main causes of VI. The eCSC was 35.1%, the eREC for distance was 40.0%, and the eREC for near was 35.7%.

Conclusion: VI remains a challenge in Odisha, as the prevalence is high and the surgical coverage is poor. Nearly 90% of VI is avoidable indicating that targeted interventions are required to address this problem.

Keywords: Blindness; Cataract; Refractive Error

J Ophthalmic Vis Res 2023; 18 (2): 182–191

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Received: 06-01-2022 Accepted: 06-11-2022

Access this article online

Website: https://knepublishing.com/index.php/JOVR

DOI: 10.18502/jovr.v18i2.13185

How to cite this article: Bhardwaj A, Vashist P, Senjam SS, Gupta V, Gupta N, Manna S. Rapid Assessment of Avoidable Visual Impairment in Two Coastal Districts of Eastern India for Determining Effective Coverage: A Cross-Sectional Study. J Ophthalmic Vis Res 2023;18:182–191.

INTRODUCTION

Vision impairment (VI), including blindness, is an alarming global public health issue with a disproportionately larger prevalence in low- and middle-income countries (LMICs). As per the recent WHO estimates, globally, approximately 2.2 billion people have near and distance VI of which almost 50% need either prevention or treatment measures.[1] In October 2019, WHO launched the first World Report on Vision to draw attention to the increasing need for eye care.[2]

India has the second largest population in the world with nearly 4.8 million of the population suffering from blindness and 74 million experiencing VI.[3] Cataract and uncorrected refractive errors (URE) are the two commonest reasons for VI in India.[3] In a country like India, where the population is diverse and heterogeneous, it is imperative to have regionally representative, valid, and robust public health data so that appropriate public health strategies can be planned at the local level. Rapid assessment of VI (RAVI) surveys are less expensive and less time-consuming as compared to detailed and resource-intensive epidemiological studies. For tracking progress at country and regional levels, RAVI surveys are needed at periodic intervals to assess baseline status and progress toward targets. Effective refractive error coverage (eREC) and effective cataract surgical coverage (eCSC) are also tracer indicators that gauge the eye care scenario in a country.[4] The global targets include a 30% increase in eCSC and a 40% increase in eREC, by 2030.[4, 5]

RAVI surveys have been completed in many areas of southern, western, central, and northern India; however, relevant data on the magnitude of the VI burden, especially in the remote underprivileged population from Eastern India is missing. A RAVI study was conducted in the population aged 40+ in two coastal districts of Odisha with the purpose of assessing the magnitude and causes of VI in the two districts and to determine the levels of eCSC and eREC in the study population.

METHODS

Two coastal districts were selected in the state of Odisha: Ganjam which is predominantly rural and Khordha which is predominantly urban.[6, 7] The sample size of 2100 per district was selected using a prevalence of 15% VI in the 40+ age group, a relative precision of 15%, confidence interval (CI) of 95%, 1.75 design effect (cluster size 70), and a nonresponse rate of 20%.[8] The study protocol was reviewed and approved by Institute Ethics Committee of All India Institute of Medical Sciences, New Delhi, India under the approval number IEC-562/02.12.2016,RP/8/2016, OP-10/06.03.2020. In addition, the protocol of the study complied with the guidelines for human studies and the World Medical Association Declaration of Helsinki.

Sampling was done in multiple stages using cluster random techniques. In urban regions of India, the district is divided into municipal wards, whereas in the rural areas the administrative divisions are villages. A list of all the municipal wards and villages in the district was obtained from the Census Office, India. In the first stage of sampling, all the subdivisions were selected, and within each subdivision, a list of 30 PSUs (primary sampling units) comprising of urban wards and villages was chosen based on the probability proportionate to size (PPS) techniques. The PSUs had a maximum population size of 2000. If a village or ward had a population greater than 2000, it was divided into smaller PSUs of size 2000, each of which was independently entered into the sampling frame. Within each PSU, the selection of households involved a compact segment sampling technique in which the selected PSU was divided into multiple segments of 300–500 people and one such segment was chosen randomly by a draw of chits. In the selected segment, the survey proceeded from one corner and all contiguous houses were visited until 70 people were enumerated. By covering a total of 30 such segments, the target sample of 2100 in each district was achieved.

The sample population comprised of all those who were aged 40+ and were habitual residents of the selected districts (living in the area for at least six months). Two teams were dispatched to visit 30 clusters in each district. Before the commencement of the study, a two-day training was given to the team regarding standard study protocols, method of cluster selection and coding, enumeration methods, clinical examination, and barrier information. Inter-observer variations among the optometrists for clinical diagnosis,

distant and near vision examinations were checked in the clinic and community. The inter-observer agreement was good (kappa > 0.8) for all survey procedures among optometrists as each team consisted of members from local areas who were helpful in overcoming any language or cultural barriers.

The survey was conducted using the standard RAVI questionnaire. It captured data on the avoidable reasons for blindness and VI in people aged 40+. This questionnaire was modified from the standard RAAB (Rapid Assessment of Avoidable Blindness), and had extra sections for near vision, use of glasses, and unaided visual acuity.

Presenting binocular near vision was measured using a simplified "E" chart having N60 and N6 optotypes with five letters in one line. The procedure was performed at a distance of 40 cm, which was ensured by using a headband attached to a rope 40 cm in length. Near vision was calculated first using the N60 optotype and then using the N6 optotype. The criterion for determining the category of vision at a certain level was selection of four correct letters out of five from the simplified "E" chart.

Distance visual acuity (VA) was tested utilizing tumbling "E" charts both with and without spectacles. VA was examined with "E" Snellen optotypes of different sizes for VA of 6/12, 6/18, and 6/60 at 6 m. The criterion for measuring vision at any of the levels was the selection of four correct answers consecutively, or four correct out of five tumbles. If the person wore spectacles for distance vision, the pinhole was placed in front of the spectacles. The lens assessment was done in an undilated pupil with a pen torch [Figure 1].

The primary outcome measure was VI, which was defined as presenting visual acuity (PVA) < 6/12 according to the International Classification of Diseases (ICD-10 as revised by WHO)).[9]

The main cause of PVA < 6/12 was separately ascertained for each eye, and the more avoidable cause was taken as the diagnosis for each person. In cases with multiple causes for VI, the disease that was more preventable/amenable to treatment to achieve VA ≥ 6/12 was considered as the principal cause. The data entry was done in specially designed Epi-data 3.1-based database with all checks in place for validation and data consistency. Double data entry was done to minimize errors and data cleaning was done to remove all inconsistent findings and outliers. Data analysis was done using the Stata 15.1 software package (Stata Corp., College Station, Texas, USA). Age and gender disaggregated prevalence of VI along with 95% CI were calculated. Univariate and multivariate analyses were done to find factors associated with VI. The sample prevalence (unstandardized) was directly standardized using the age-sex distribution of the combined population of the two districts, using Stata software. Association of VI with age, gender, education, and locality was checked by using multiple logistic regression analysis.

RESULTS

Overall, 4200 individuals aged 40+ were enumerated, of whom 3745 (89.2%) were examined. The number of males was 1677 (44.8%) and that of females was 2068 (55.2%). The response rate was better among females (91.6%) than males (86.4%), as far as clinical examination was concerned. Out of the 455 not examined, 441 were either not available or were unable to communicate and 14 refused to undergo examination. There was no significant difference between the socio-demographic profile of the sample and target population (Odisha state) (P = 0.57) [Table 1].

The age and sex standardized prevalence of VI including blindness was 12.77% (95% C.I. 11.85–13.69). Although the prevalence of VI (including blindness) was higher in males (16.33%, 95% CI: 14.56–18.11) than females (14.74%, 95% CI:13.21–16.27), the difference was not statistically significant (P = 0.181). The standardized prevalence of moderate VI (MVI: presenting visual acuity <6/18 to 6/60 in the better eye) and severe VI (SVI: presenting visual acuity <6/60 to 3/60 in the better eye) in study subjects was 4.84% and 1.13%, respectively. The blindness prevalence in the study population was 1.14% (95% C.I. 0.84–1.45) [Table 2].

The prevalence of VI and URE exhibited a rising trend with age. Maximum VI (including blindness) was seen in females above the age of 80 years (68.3%) [Figure 2 & Table 3]. Out of the 3745 study participants, 343 (9.2%) had URE. Another 155 (4.1%) had corrected refractive errors (RE) giving a total of 498 individuals with any form of RE (13.3%).

Table 1. Socio-demographic profile of 40+ sample population in Khordha and Ganjam districts compared with Odisha state.

Variable	Sample			Odisha		
	Male (%)	Female (%)	Total (%)	Male (%)	Female (%)	Total (%)
Age groups (yr)						
40–49	449 (26.7)	705 (34.1)	1154 (30.8)	26,00,286 (41.3)	24,25,218 (40.1)	50,25,504 (40.7)
50–59	438 (26.1)	550 (26.6)	988 (26.4)	17,01,815 (27.0)	16,29,717 (26.9)	33,31,532 (26.9)
60–69	440 (26.2)	510 (24.7)	950 (25.4)	12,25,484 (19.5)	12,28,102 (20.3)	24,53,586 (19.9)
70–79	260 (15.5)	240 (11.6)	500 (13.4)	5,63,929 (8.9)	5,68,941 (9.4)	11,32,870 (9.2)
≥80	90 (5.4)	63 (3.0)	153 (4.1)	2,04,857 (3.3)	1,93,135 (3.2)	3,97,992 (3.2)
Total	1677	2068	3745	62,96,371	60,45,113	1,23,41,484
Education						
Illiterate	274 (16.3)	917 (44.3)	1191 (31.8)	18,76,376 (29.8)	36,96,032 (61.2)	55,72,408 (45.2)
Up to 4^{th}	380 (22.7)	548 (26.5)	928 (24.8)	12,06,268 (19.2)	8,34,639 (13.8)	20,40,907 (16.6)
5^{th}–9^{th} pass	419 (24.9)	351 (16.9)	770 (20.6)	18,98,155 (30.2)	10,83,901 (17.9)	29,82,056 (24.2)
>10^{th} pass	604 (36.0)	252 (12.2)	856 (22.9)	13,06,345 (20.8)	4,24,874 (7.0)	17,31,219 (14.0)
Total	1677	2068	3745	62,87,144	60,39,446	1,23,26,590

Table 2. Prevalence of visual impairment and blindness among 40+ population in Khordha and Ganjam districts of Odisha.

		Combined % (95% CI)					Unstandardized prevalence (%)	Standardized prevalence (%)
	Definition	Male (N = 1677)		Female (N = 2068)		Total		
Blind	PVA < 3/60 in BE*	27	1.61 (1.00–2.21)	27	1.30 (0.81–1.79)	54	1.44 (1.06–1.95)	1.14 (0.84–1.45)
SVI	PVA < 6/60 – 3/60 in BE*	23	1.37 (0.81–1.93)	30	1.45 (0.93–1.96)	53	1.41 (1.15–1.73)	1.13 (0.83–1.43)
MVI	PVA < 6/18 – 6/60 in BE*	107	6.38 (5.20–7.55)	113	5.46 (4.48–6.44)	220	5.87 (5.10–6.75)	4.84 (4.22–5.46)
Mild VI	PVA < 6/12 – 6/18 in BE*	117	6.97 (5.75–8.19)	135	6.52 (5.46–7.59)	252	6.72 (5.74–7.86)	5.64 (4.96–6.33)
VI	PVA< 6/12 in BE*	274	16.33 (14.56–18.11)	305	14.74 (13.21–16.27)	579	15.46 (14.06–16.96)	12.77 (11.85–13.69)

*PVA, presenting visual acuity; BE, better eye with available correction or with best correction or pinhole (BCVA or PINVA); SVI, severe visual impairment; mvi, moderate visual impairment; VI, visual impairment; CI, confidence interval.

Table 3. Age-wise prevalence of visual impairment and uncorrected refractive error among 40+ population in Khordha and Ganjam districts of Odisha.

Age group (yr)	Prevalence of VI (PVA < 6/12 in better eye) (%)								Prevalence of uncorrected refractive error (%) with 95% CI
	Male	Prev (%)	Female	Prev (%)	Total	Prev (%)	Odds ratio	P-value	
40–49	11	2.4	20	2.8	31	2.7	1	0.000	3.1 (2.19–4.29)
50–59	44	10.0	37	6.7	81	8.2	3.28 (2.15–5.00)	0.000	7.7 (6.11–9.53)
60–69	83	18.9	106	20.8	189	19.9	9.06 (6.13–13.38)	0.000	14.4 (12.25–16.82)
70–79	82	31.5	99	41.2	181	36.2	20.38 (13.65–30.42)	0.000	14.2 (11.26–17.57)
80+	54	60.0	43	68.3	97	63.4	62.75 (38.62–101.95)	0.000	15.0 (9.77–21.70)
Total	274	16.3	305	14.7	579	15.5			9.2 (8.25–10.13)

*Prev, prevalence; VI, visual impairment; CI, confidence interval; PVA, presenting visual acuity

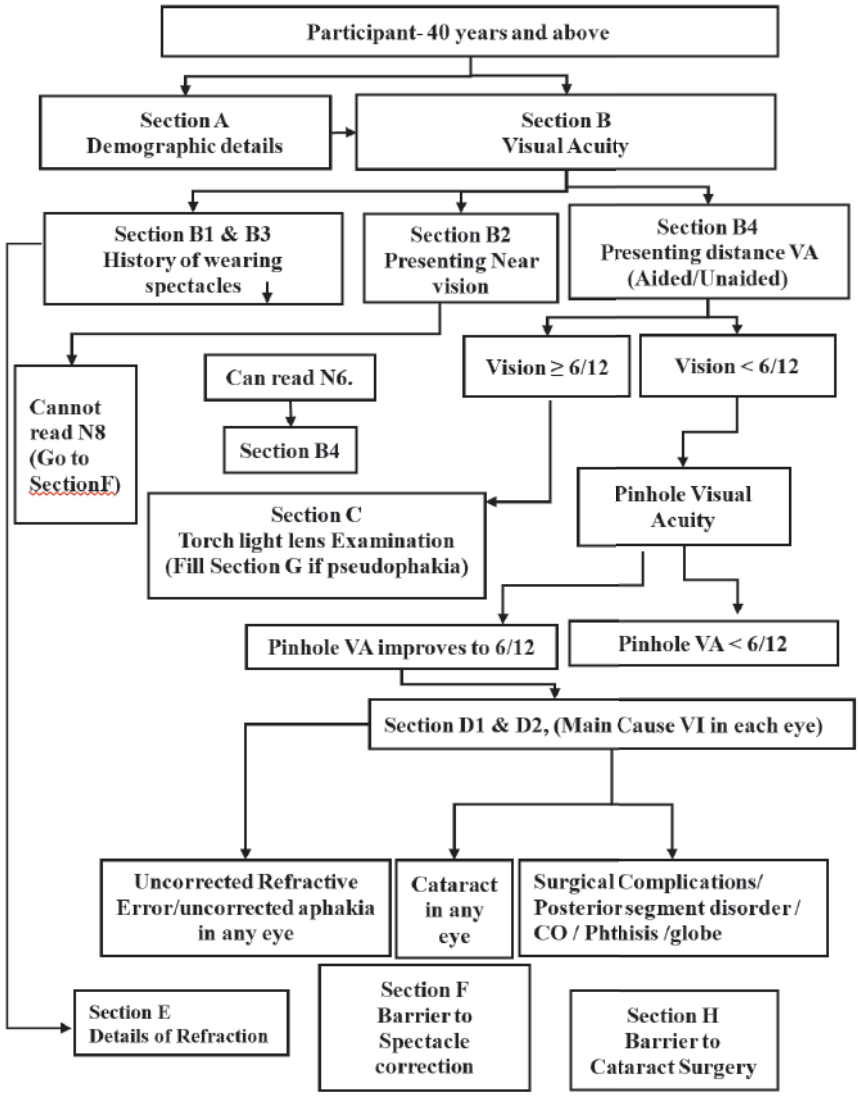

Figure 1. Examination protocol of the RAAVI Study in Khordha and Ganjam districts of Odisha.

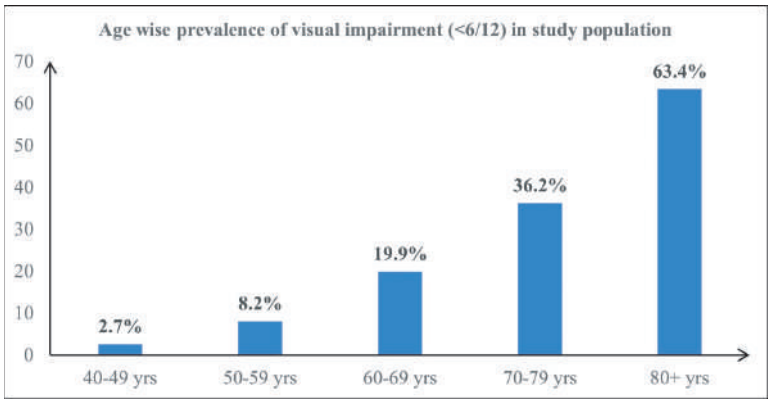

Figure 2. Age-wise prevalence of visual impairment among 40+ population in Khordha and Ganjam districts of Odisha.

Table 4. Cataract surgical coverage and effective coverage among 40+ population in Khordha and Ganjam districts of Odisha.

CSC (persons)	Male (%)	Female (%)	Total (%)
PinVA < 3/60	88.29	88.11	88.19
PinVA < 6/60	84.30	79.88	81.72
PinVA < 6/18	66.67	59.83	62.74
PinVA < 6/12	49.08	46.04	47.40
eCSC	33.70	36.09	35.02
eREC for distance	38.10	41.91	40.08
eREC for near	40.01	32.83	35.65

*CSC, cataract surgical coverage; PinVA, pinhole visual acuity; eCSC, effective cataract surgical coverage; eERC, effective refractive error coverage

Table 5. Multiple logistic regression analysis for finding determinants of visual impairment in Khordha and Ganjam districts of Odisha.

Variable	Odds ratio	95% Confidence Interval	z-value	P-value
Age groups (yr)				
40–49	1			
50–59	3.07	2.00–4.69	5.16	<0.001
60–69	7.71	5.16–11.51	9.97	<0.001
70–79	16.48	10.86–25.03	13.15	<0.001
≥80	51.19	30.61–85.60	15.00	<0.001
Gender				
Male	1			
Female	0.79	0.64–0.99	–1.98	0.048
Locality				
Rural	1			
Urban	1.26	1.02–1.57	2.18	0.03
Education				
Illiterate	1			
Up to 4^{th}	0.62	0.48–0.81	–3.53	<0.001
5^{th}–9^{th} pass	0.62	0.45–0.84	–3.09	0.002
>10^{th} pass	0.39	0.27–0.56	–5.04	<0.001
Use of distance glasses				
No	1			
Yes	0.31	0.46–0.21	–5.84	<0.001

*RAAVI, rapid assessment of avoidable visual impairment; VA, visual acuity; VI, visual impairment; CO, corneal opacity.

Prevalence of URE among males was 9.5% (95% CI: 8.12–10.99) and among females was 8.9% (95% CI: 7.71–10.21); the difference was not significant (*P* = 0.538) [Table 3]. The prevalence of VI in rural participants was 16%, which was higher than that of urban participants (14.6%). Cataract was the single most important cause of blindness (72.2%) and VI (62.7%) in this region [Figure 3].

A total of 536 cataract surgeries were reported among people from the study population. More

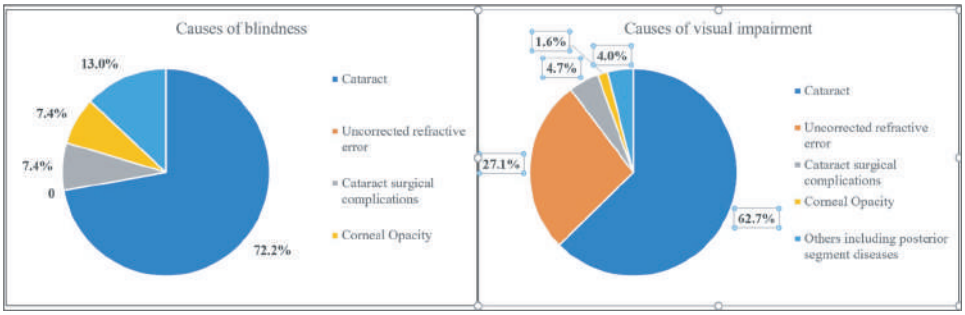

Figure 3. Causes of blindness and visual impairment (PVA < 6/12 in better eye) among 40+ population in Khordha and Ganjam districts of Odisha.

females reported surgery (288) as compared to males (248). The proportion of surgeries with an intraocular lens (IOL) implant was 94.0%. Out of the 377 persons (536 eyes) who underwent cataract surgery, 159 were bilaterally operated while 218 had undergone unilateral cataract surgery. It was observed that the majority of unilateral and bilateral cataract surgeries were performed in people aged 60 years and above.

When visual outcomes were assessed in the operated eye, it was seen that 355 eyes (66.2%) had very good outcomes (≥6/12), 54 (10.1%) had good outcomes (<6/12 to 6/18), 57 (10.6%) had borderline outcomes (<6/18 to 6/60), and 70 (13.1%) had poor outcomes (<6/60). Poor outcomes were caused by operative complications in 50 (71.4%) eyes, ocular comorbidity in 18 (25.7%), and RE in 2 (2.9%) eyes. Nearly half of the surgeries, that is, 253 (47.2%) were performed in the last five years. The visual outcomes were better among surgeries reported in the last five years as compared to surgeries performed before that, and the difference was statistically significant (P = 0.014). The CSC (Cataract Surgical Coverage) in two districts of Odisha for 40+ population was 47.4% by 6/12 cut-off and 88.19% for pinhole vision <3/60. The eCSC was 35.1%, eREC for distance was 40.0%, and eREC for near was 35.7% for the same population [Table 4].

Out of the 536 cataract surgeries, 300 (55.9%) took place in non-governmental organizations (NGO)/private sector as compared to 236 (44.0%) in the public sector, and 287 (53.5%) of the surgeries were paid irrespective of the place of surgery.

The usage of distance glasses was reported by only 518 (13.8%) study participants (males 265 [15.8%] and females 253 [12.2%]). Similarly, near glasses were being used by only 666 (17.8%) participants (males 364 [21.7%] and females 302 [14.6%]). Out of a total of 735 participants who received refraction services, 505 (68.7%) had their last refraction more than two years back. Most refractions, that is, 557 (75.8%) took place in the NGO/private sector (males 74.7% and females 77.3%). The majority (89.7%) of participants reported having to pay for their glasses irrespective of place of refraction.

Barriers to not wearing glasses among those who were identified as having URE/presbyopia or uncorrected aphakia were assessed. The most common barriers were need not felt (57.5%), financial constraints (13.8%), uncomfortable glasses (8.2%), various local reasons like no one to accompany them, and other personal preoccupations (11.0%) in addition to lack of awareness (5.0%).

Multiple logistic regression was done to find determinants of VI in the study population. The odds of VI increased significantly in higher ages and were greater among the urban population (OR 1.2; 95% CI 1.0–1.6). Being educated (OR 0.4; 95% CI 0.3–0.6) and use of glasses (OR 0.3; 95% CI 0.5–0.2) were protective. All these risk factors are well-established as associated with VI [Table 5].

DISCUSSION

The current study utilized the novel RAVI methodology to determine the prevalence and causes of VI in two districts of Odisha, India. According to the National Blindness Survey (NBS), the prevalence of blindness in the 50+ age population in India was 1.99% and cataract (66.2%) was the most important cause of blindness followed by corneal opacity (8.2%).[10]

In the current study, the age-sex-adjusted prevalence of blindness was 1.14%; MVI was 4.84%, and VI was 12.77% among the 40+ age population in Odisha. The NBS was conducted among the 50+ age population in one district of Odisha (Nayagarh) and the prevalence of blindness and MVI reported were 1.77% and 13.4%, respectively.[3, 10] Although the prevalence figures in the current study are lower as compared to NBS, it might be due to the lower age group (40+) and other differences among the survey participants. Despite this, the VI due to cataract and RE needs to be managed promptly as the study clearly highlights poor coverage for cataract and RE services in Odisha.

The study demonstrated that the risk of VI increased significantly with age, which is being corroborated by numerous studies done in both South and North India.[8, 11, 12] A previous study on blindness had reported that females were at 1.41 times higher risk of blindness in urban areas and 1.51 times in rural areas, compared to their male counterparts.[13] However, no significant difference was observed by gender in the current study. Cataract is a major cause of VI and blindness in the current study. These findings are similar to the findings from South India.[14] Cataract and REs combined contributed to >90% of VI both of which are amenable to treatment as compared to the other causes. Cataract surgery has been identified as surgical intervention that costs <$200 per disability-adjusted life years averted.[15]

The CSC of Odisha for the 40+ age population was determined as 47.4%. In the NBS, a CSC (persons) of 50.0% at a VA cut-off of 6/18 was reported in Nayagarh, Odisha.[3] Another RAAB study by SightSavers in the Kalahandi district of Odisha reported a CSC of 45.5%.[16] In both studies, males had higher CSC than females, similar to the findings of the current study. A study from rural Northern India reported higher CSC in females than males, with CSC of 43.2% at 6/60 cut-off.[17] Lower CSC and thereby higher prevalence of cataract and VI was observed in rural areas in many countries.[18, 19] The eCSC determined in the current study was 35.02% and it was higher in females as compared to males. Very few studies have reported eCSC from the Indian subcontinent. A preliminary analysis (unpublished) of 47 population-based surveys from 11 countries revealed a significant range in eCSC between countries, from 2.8% to 88.5%.[4] Data from repeated population-based surveys within four LMICs revealed an average annual percentage point increase in eCSC of 1.1% (range = 0.8% - 1.4%). In addition, gender inequities in eCSC have been reported: it is estimated that globally, women were 1.21 times more susceptible to having cataract VI as compared to men, and the mean level of inequality amongst women in eCSC is 4.6%.[20, 21]

In order to know the exact number of people with VI due to RE, uncorrected visual acuity needs to be measured, that is, without spectacles or contact lenses.[4] The current study employed this methodology, and the prevalence found was 9.2%. In the current study, the eREC for distance was 40.1%, while for the near vision it was 35.6%. Rates of eREC for near is lower than 20% in sub-Saharan Africa, while the same figures in North America are reported to be higher than 90%.[22]

The impact of REs is manifold and includes loss of livelihood, schooling, and financial resources.[23] Estimates of global economic burden of distant VI due to URE is huge (US$ 202 billion).[24] Globally, nearly 800 million people suffer from distance VI (i.e., myopia and hypermetropia) or near VI (i.e., presbyopia) who need just a pair of spectacles, while another 100 million persons have moderate-to-severe distance VI or blindness that is amenable by cataract surgery.[25] The sustainability of programs for treatment of cataract and RE need huge expenditure in terms of equipment, manpower, and spectacles. Hence, sale of customized spectacles can also be explored as an alternative source of revenue by hospitals that want to scale-up their cataract surgical and refractive services, as envisioned by the Vision 2020 Right to Sight Initiative. The Government of India launched the National Program for Control of Blindness and Visual Impairment (NPCB&VI) in 1976 and it currently has the provision of free services for cataract and other subspecialties; however, with the increase in the number of RE, there is a need to introduce a provision of subsidized/free spectacles also into the program to alleviate some of the additional costs ensued.[26] Generation of demand for services and addressing various barriers for accessing those services is necessary to scale-up the provision of cataract surgical and refractive error services to the population.

The WHO has given targets for achieving universal eye health coverage (UHC) by 2030, that is, a 30% point increase in eCSC and 40% increase in eREC from baseline.[4] This means that Odisha

needs to achieve an eCSC and eREC of 65.0% and 80.1%, respectively, by 2030, from the baseline figures reported in the current study. This can be possible only if the management of VI is prioritized in Odisha in a systematic way. Shortage of trained human resources and resource constraints are always bottlenecks for such ambitious targets. The National Program for Control of Blindness and Visual Impairment (NPCBVI) can provide effective RE and cataract surgical services free of cost or at subsidized rates, which can be incorporated in the health insurance packages available to the people.

The current RAAVI study has a few limitations. First, it is not adequately powered to determine the prevalence of blindness. The sample size was deduced based on the prevalence of VI in previous studies and would only provide accurate estimation of the prevalence of VI. Second, the findings of the study cannot be extrapolated to other districts of Odisha, and separate surveys need to be conducted in each of the districts to accurately gauge the magnitude of the problem in the entire state. The burden of VI needs prompt attention in Odisha, majority of which is caused by cataract and RE. The findings suggest that the absolute number of people susceptible to avoidable blindness is enormous, and free or subsidized cataract and RE services is the need of the hour. It is hoped that this baseline study from Odisha will be instrumental in planning eye care services in the state in the future. Some of the major recommendations from the current study include, graded scaling up of cataract and RE services over the next decade to achieve UHC targets by 2030, reducing cost of services by incorporating services in insurance packages and prioritizing vulnerable individuals like the elderly, illiterate, and urban poor. RAAVI studies need to be conducted in all the districts of Odisha, and district-specific interventions need to be planned.

Ethical Considerations

The study protocol was reviewed and approved by Institute Ethics Committee of All India Institute of Medical Sciences, New Delhi, India under the approval number IEC-562/02.12.2016,RP/8/2016, OP-10/06.03.2020. In addition, the protocol of the study complied with the guidelines for human studies and the World Medical Association Declaration of Helsinki. A participant information sheet (PIS) in local language Odia was given to each participant. In case of illiterate or visually impaired participants, the PIS was read out to the participant. Written consent was obtained from each participant before they were included in the study. In case of illiterate persons, left thumb impression was obtained. Participants who were identified with treatable or curable conditions were provided referral services to the nearest secondary/tertiary eye hospital.

Acknowledgements

Dr. Sabyasachi Pattanayak from DHS Odisha and Lt. Dr. Mihir Bal from ECOS Eye Hospital, Brahmapur.

Financial Support and Sponsorship

Financial support for this study was provided by CBM, India. Consent for publication was taken according to the ICMJE recommendations for protection of research participants.

Conflicts of Interest

None.

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Original Article

Eye Care in Young Children: A Parents' Perspective of Access and Barriers

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Abstract

Purpose: To evaluate parental perspectives of accessing eye care for children aged under seven years.

Methods: The survey was conducted during September 2020 to March 2021 using online applications and distributed to parents whose children were between the ages of three and seven years. The survey included parents' background, their knowledge of the provision of eye-care services, and the possible barriers that existed to access eye-care services. The relationship between parents' knowledge, barrier scores, level of parental education, and demographic or socioeconomic status was assessed using nonparametric tests.

Results: In total, 1037 questionnaires were completed. The respondents were from 50 cities across Saudi regions. The participants' age was 39 ± 7.5 years, and 54% of them had at least one child under the age of seven (n = 564). Further, 47% had not taken their children for vision screening at reception/year one (n = 467). In addition, 65% of them were not aware of the mandatory screening program at reception/year *1*; whereas, only 20% (n = 207) knew how to access eye-care services; and only 39% of the children had undergone any kind of eye or vision test. The pathways to eye care and the cost of eye services/glasses were the main limitations. The parents' responses were significantly influenced by their demographic and socioeconomic characteristics (Kruskal Wallis, $P < 0.05$).

Conclusion: There was a need for enhancing parent information on how to access eye care for young children and the currently available vision screening programs. Finally, a national protocol to cover the cost of the eye exam as well as spectacle prescription shall be proposed as a mean of incentive.

Keywords: Amblyopia; Refractive Errors; Saudi Arabia; Strabismus; Vision Disorders; Vision Screening

J Ophthalmic Vis Res 2023; 18 (2): 192–201

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Received: 04-04-2021 Accepted: 10-11-2022

How to cite this article: Alsaqr AM. Eye Care in Young Children: A Parents' Perspective of Access and Barriers . J Ophthalmic Vis Res 2023;18:192–201.

Access this article online

Website: https://knepublishing.com/index.php/JOVR

DOI: 10.18502/jovr.v18i2.13186

INTRODUCTION

A great number of population-based studies have indicated that the main visual disorders in children are refractive errors, amblyopia, and strabismus.[1–12] Early proactive interventions for reduced vision are predominantly important during this critical period of visual development in children and should be started as early as possible.[7, 13] Reduced visual acuity has marked implications on education, health, social outcomes, and quality of life of affected children.[14–20] If untreated or not detected early, these disorders would eventually lead to amblyopia and visual impairment.[21, 22] Furthermore, in 2007, it was estimated that uncorrected refractive errors have a global economic burden of approximately $269 billion per annum because of productivity losses.[23] Specifically, several studies have stated the importance of vision screening in children under seven years old.[10, 20, 24] These children are at risk of functionally low vision.[25, 26]

In the agenda of VISION 2020 (The Right to Sight), the World Health Organization set the management of childhood visual disability as a priority.[27] The American Academy of Pediatrics, the American Association for Pediatric Ophthalmology and Strabismus, and the American Academy of Ophthalmology have also set a joint policy statement on child vision screening.[27] Preschool vision screening policies vary due to differences in the policies that exist in countries.[13, 16, 17, 26] In Saudi Arabia (SA), according to government laws, the Ministry of Education requires an obligatory medical examination, which includes an assessment of visual acuity for all school entrants.[28] However, it is observed that examination facilities may be inadequate.[11]

Interested individuals involved in preschool vision screenings include parents, school teachers, and health professionals (optometrists, ophthalmologists, etc.). The perception, awareness, and level of accepted responsibilities of these individuals could play a crucial role in the efficacy of child vision screening programs and the development of policies for school and preschool-age children.[24, 29–31] A study conducted in England reported that approximately 30% of children did not attend follow-up visits after failing screening tests at schools' entry year.[9] Several studies have emphasized the importance of parents' awareness in combating children's visual problems.[29–32] The parents' knowledge of the potential visual disorders at younger age and receiving the screening outcome of children who failed visual screening could be essential for seeking health counseling.[18, 29, 32] Specifically, parents as caregivers play the fundamental role in seeking eye-care services for their children to avoid experiencing visual disorders that may go untreated.[33] Parents' socioeconomic status could also pose as an important factor when accessing eye-care services.[8, 34, 35]

To date, very few studies have been done on accessibility and barriers to eye care for children in SA, and generally in the Middle East region. The problems outlined through this research is of critical importance toward understanding the extent and complexity of the challenges facing policy makers and eye-care professionals. This knowledge gap provided an opportunity to establish a point of reference as compared to other studies conducted in other worldwide countries.[7, 31, 32, 36–38] Therefore, this study evaluated parents' knowledge of how to access eye care and what barriers might disable them from accessing eye care for their children.

METHODS

The study protocol was reviewed and approved by the IRB ethical committee of King Saud University, Saudi Arabia, and the approval number is E-22-7412. In addition, the protocol of the study complied with the guidelines for human studies and the World Medical Association Declaration of Helsinki, and parental consent was electronically obtained before filling out the questionnaires. In order to ensure transparency and to receive honest responses from participants, information and aims of the survey were absolutely and clearly described to the parents at the beginning of the survey.

This study is cross-sectional in design and targeted toward the parents of children under seven years of age in different regions of SA. The survey used in this study was adapted from a previously published study.[32] The survey involved parents' demographic data, general medical and ocular history, and their knowledge and barriers regarding accessing eye-care services.

To compute the required sample size, we used Epi Info, version 7 (Centers for Disease Control, Atlanta, GA, USA; http://wwwn.cdc.gov/epiinfo/7/),

and the number of children under seven years in SA were approximately 6 million.[39] Furthermore, in the calculation, 95% confidence intervals, an expected frequency of 50%, a design effect of 2, and the number of clusters of five regions (central, northern, western, eastern, and southern regions) were included. The overall sample size was estimated to be 760 parents. The sample was expected to be unequal in each cluster but proportionate to the number of inhabitants in each region as they differed to a large extent (e.g., central region has approximately 8 million inhabitants and there are approximately 2 million inhabitants in the northern region). The survey was promoted for about six months (from September 2020 to March 2021) in order to recruit sufficient participants representing the Saudi population.

The survey used an online questionnaire, which was accessible without any restrictions. Emails were sent to the members of the Saudi Optometry Society to promote the survey in their areas using all accessible legal means, and the survey was distributed using all available social media applications (e.g., Twitter, WhatsApp, and Telegram). To avoid duplicate responses, at the beginning of the survey, a note was placed stating that responding to the survey more than once is prohibited. Lastly, the raw responses were properly reviewed and checked for duplication and to detect the parents who did not have children under seven years old, and eventually, 125 responses out of the 1162 initial ones were excluded.

Data were explored for normality using the Kolmogorov–Smirnov test, which indicated that the data was not normally distributed. Therefore, the nonparametric Kruskal–Wallis test was performed to consider any possible relationship among the factors of parents' knowledge, barrier scores, level of parental education, and demographic or socioeconomic status. Data were collected in Excel (Microsoft Corporation, Redmond, WA, USA) and analyzed using the Statistical Package for the Social Sciences (IBM Corp., Armonk, NY, USA).

RESULTS

The number of participants was 1037, with 83% (*n* = 861) being mothers. Most participants were married (96%, *n* = 995), and the rest were either divorced or widowed (2% for each category). The participants were recruited from across five regions, involving 50 cities.

Parents' Background Characteristics

The participants' mean age was 39 ± 7.5 years and their educational level ranged from dropout (people who left school at the age of 16 years without formal degree) to Doctor of Philosophy (PhD) degree [Figure 1]. The participants' occupations were diverse – unemployed, civil employees, teachers, health professionals, security forces, entrepreneurs, and assistant executive officers. In terms of their monthly incomes, the responses ranged from under $1400 to >$8000 [Figure 2]. None of them had more than four children (one child: 564 [54%], two children: 407 [39%], three children: 75 [6%], four children: 15 [1%], respectively). Additionally, 18% (*n* = 187) had a general medical history (e.g., systemic hypertension, diabetes, asthma, thyroid gland dysfunction, and back pain). Lastly, approximately 33% of the participants reported some form of ocular disorder (e.g., refractive error, dry eye, cataract, keratoconus, amblyopia, and diabetic retinopathy).

Parents' Eye Care-seeking Behavior

Interestingly, about half of the parents (467, 45%) responded that they had not taken their children to a vision screening at the entry of reception/year one. When asked if they were aware of the mandatory vision exam at the entry of reception/year one, 65% of the parents' responded with "NO" and another 13% with "maybe". The parents' responses to questions directed toward the current visual status are summarized in Table 1. Regarding children who refused an eye test, only seven parents reported that they were given a reason for not being provided the service [Table 1]. Reasons included poor cooperation, young age, cost of service, waiting time, and presence of autism in a child.

The survey also checked to understand the reasons why parents would consider seeking eye care for their children. Their responses varied across different reasons as listed in Table 2. Some participants reported other reasons for intentionally seeking eye care, including excessive use of electronic devices, dry eyes, juvenile

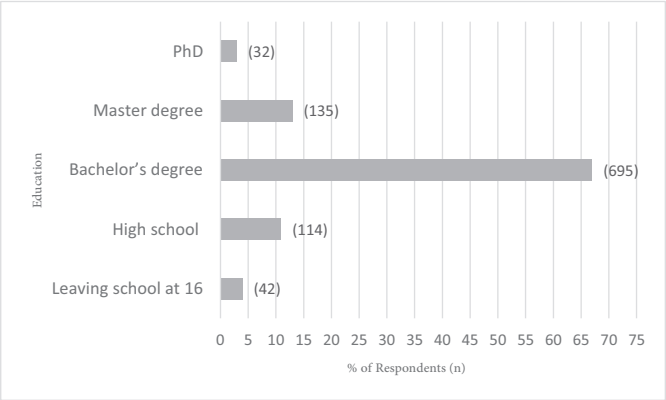

Figure 1. Respondents' education profiles, Saudi Arabia in year 2021.

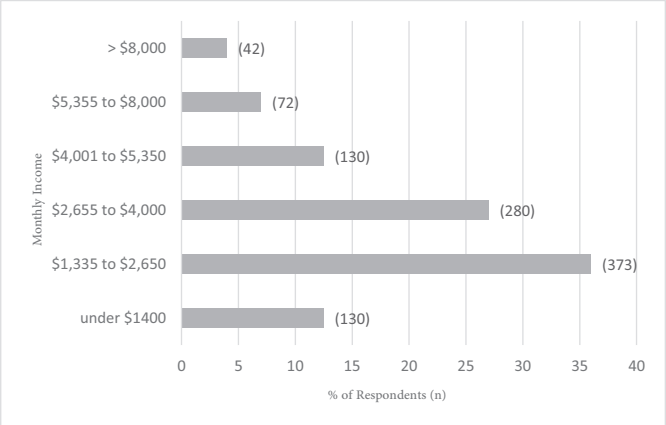

Figure 2. Respondents' monthly income profiles, Saudi Arabia in year 2021.

Table 1. Parental responses to the questions on the current visual status of their children, Saudi Arabia in year 2021.

Query	Yes (n, %)	No (n, %)	Not sure (n, %)
Routine vision screening in child's school	99, 9.5%	793, 76.5%	145, 14%
Concerns about child's eyes or vision	436, 42%	441, 42.5%	160, 15.5%
Know how to access an eye test appropriate for your child's age	207, 20%	778, 75%	52, 5%
Child's close family members who wear glasses and have a lazy eye or an eye turn	736, 71%	259, 25%	42, 4%
Has child ever had any kind of eye or vision test?	405, 39%	601, 58%	31, 3%
Has child ever been refused an eye test?	36, 3.5%	990, 95.5%	11, 1%
From previous question, what reason was given if an eye test was refused?	7 of 36, 19.5%	21 of 36, 58%	8 of 36, 22%

Table 2. Parental responses to the question stating, "For what reasons would you consider seeking an eye examination for your child?" The parents were allowed to choose more than one choice, Saudi Arabia in year 2021.

Inquiry	Response (n,%)
Advised by healthcare provider or teacher	347, 33.5%
Concerns about poor vision	550, 53%
Concerns about eyes not being straight/having an eye turn	249, 24%
Headaches	239, 23%
Poor concentration/short attention span	300, 29%
Poor school achievement and/or difficulties with literacy	224, 22.50%
Complaints of double vision	166, 16%
Routine checkup	353, 34%
Family history	322, 31%
Others	36, 3.50%

Table 3. Parental responses toward questions directed to existing knowledge about child vision and vision screening, Saudi Arabia in year 2021.

Query	Agree (n, %)	Disagree (n, %)	Not sure (n, %)
Children can only have an eye test when they know the names of the letters	207, 20%	498, 48%	332, 32%
Wearing glasses if you need them when under age of seven years will make your eyes and vision stronger	492, 47.5%	166, 16%	379, 36.5%
It is normal for a child aged one to seven years to occasionally have an eye turn	264, 25.5%	332, 32%	441, 42.5%
School vision screening tests for all eye problems	254, 24.5%	410, 39.5%	373, 36%

diabetes, eye redness, itching, and excessive blinking. In addition, the parents were surveyed based on their preexisting knowledge related to child vision and vision screening [Table 3].

Barriers to Eye Care-seeking Behavior

The parents were asked about the barriers that might prevent them from taking their children for an eye test [Table 4]. Some parents mentioned additional barriers including their beliefs that the vision of their children was normal, the child being uncooperative, and personally not seeing a reason for an eye test and challenges with time management.

Parents' Background Related to Their Knowledge and Barriers

An investigation was conducted to determine whether the responses were influenced by the parents' background or other related factors that included gender, marital status, age, income, working status, level of education, and family history of eye problems. After the investigation, it was ascertained that those characteristics influenced some of the parents' responses listed in Table 5.

DISCUSSION

This study showed that half of the parents had not taken their children for vision screening at

Table 4. Parental responses to the question stating the possible reasons that may prevent the parents from taking their children for an eye test. The parents were allowed to choose more than one choice, Saudi Arabia in year 2021.

Inquiry	Response (n,%)
I do not know how and/or where to arrange an appointment for an eye test	342, 33%
I am worried about the cost of an eye test	135, 13%
I am worried about the cost of glasses	82, 8%
I think my child is too young to have an eye test	270, 26%
I am worried my child does 'not know all the letters yet	124, 12%
I have been told that my child is too young for an eye test	52, 5%
I do not want my child to wear glasses	114, 11%
I am worried my child may be given glasses he/she does not need	218, 21%
I am worried if my child is given glasses that it will make his/her eyes weaker	156, 15%
Others	73, 7%

reception/year one. The majority of them were not even aware of the mandatory screening program. Further, only one-fifth of them knew of the pathways to access eye-care services. About 60% of the children had not undergone any kind of eye or vision test. Barriers and misconceptions related to eye-care services, which needed intensive and in-depth strategies to deal with, were detected. Participants' backgrounds and socioeconomic characteristics also played a major role in some of the parents' responses.

Accessibility to vision screening is important for the well-being of children.[10, 40] Understanding the barriers to and knowledge of accessing eye-care services for children from a parental perspective is fundamental in determining strategies and programs that enrich the parents' awareness and provide methods to direct them for the best possible access to checking the vision of their children.[32] Parental knowledge of risk factors related to not checking children's vision could contribute to early detection and management of various visual disorders, such as amblyopia and strabismus.[34, 35, 41] This would also require the cooperation of eye-care professionals.[7] In 2019, Cassetti et al suggested that it is imperative to consider parents' lack of eye health education as well as the importance of enhancing specialists' experience when treating children, and how to tackle parents' negative attitudes toward diagnosis and treatment.[7]

In this study, the percentage of parents whose children had received any kind of eye or vision test was closely similar to a report of a study in English children (45% vs 51%, respectively).[32] In comparison to another study, our findings were better than those found in Swaziland children, where 60% of their participants had never taken their children for an eye test.[38] Furthermore, concerns were raised about the efficacy of mandatory assessments at school reception/year one in light of poor awareness of the screening program, supported by the findings of Donaldson et al who reported that only 15% of the parents whose children go to a school with a screening program knew of its existence.[32] Moreover, only a few participants had been given a reason for not being provided the service, and not allowing a child to undergo vision screening could cause major consequences on the child's well-being and quality of life.[29, 42] The reasons given by healthcare workers for not providing vision screening were mainly due to a lack of cooperation by the underaged subjects, a lack of financial resources by the parents, or the patients' ailments that would require more intricate testing and evaluation. Providing more professional training, giving out vouchers for eye examinations in schools, and easing the access to eye-care services provided by governmental hospitals may be very helpful in alleviating the lack of eye care for young children.[7, 32] In agreement with previous research, parents may also need

Table 5. Influence of the participants' background characteristics on some of the parents' responses, Saudi Arabia in year 2021.

Factors	Findings	Kruskal–Wallis test
Gender	The number of children who have been tested at reception/year one in mothers' response was greater than that in males.	H (2) = 5.22; *P* = 0.02
	The mothers was higher than that of males who had been refused eye-care services for their children.	H (2) = 5.73; *P* = 0.02
Marital status	Married couples were more informed about the mandatory eye exam at reception/year one.	H (2) = 6.26; *P* = 0.04
Age	Older parents were more likely to test their children at reception/year one.	H (4) = 17, *P* = 0.001
	Older parents were more informed about the mandatory eye exam at reception/year one.	H (4) = 9.6, *P* = 0.02
	Older parents were more informed about eye tests conducted at schools.	H (4) = 7.9, *P* = 0.048
	Older parents were more likely to take their young children to eye-care service.	H (4) = 18.6, *P* < 0.0001
	Older parents were more likely to have a medical eye history.	H (4) = 22.3, *P* < 0.0001
Parents' education	The higher the parents' education, the more they know about the mandatory eye examination at reception/year one.	H (4) = 12.5, *P* = 0.01
	The higher the parents' education, the more they know about pathways on how to access eye-care service.	H (4) = 15.4, *P* = 0.004
	The higher the parents' education, the more they positively believe that using glasses, if needed, under the age of seven years will make their children's vision stronger.	H (4) = 13.7, *P* = 0.01
Parents' working status	Teachers were the most informed about the mandatory eye examination at reception/year one.	H (6) = 13.8, *P* = 0.01
	Teachers had more knowledge about the routine eye examinations performed at schools.	H (6) = 11.66, *P* = 0.02
	Teachers had more concerns about their children's vision.	H (6) = 12.7, *P* = 0.01
	Housewives accounted for the greatest number of those who believe that wearing glasses, if needed, will make their children's eyes and vision stronger.	H (6) = 10.6, *P* = 0.03
	Housewives had the most number among those not knowing how to access eye-care services.	H (6) = 11.69, *P* = 0.02
Parents' income	Children of parents who had a lesser income were the least of being tested at reception/year one.	H (5) = 11.5, *P* = 0.04
	Parents with lesser income were more likely to be refused to provide eye-care services.	H (5) = 15.2, *P* = 0.01
	Parents with lesser income were more likely to believe that it is normal for a child under the age of seven years to occasionally have an eye turn.	H (5) = 18.2, *P* = 0.003
Presence of ocular history	Parents with an ocular history tend to not test their children at reception/year one.	H (2) = 6.9; *P* = 0.01
	Parents with an ocular history have the highest response of "yes" among those who have been provided with reasons for refusing eye-care services.	H (2) = 5.5; *P* = 0.02

more health education and more effective and accessible eye-care services.[38, 43, 44]

Parental misconceptions about eye examinations for children and their vision were the main barriers to taking children for a vision test. Similar to previous research, not knowing how and where to access eye-care services and not being able to afford the cost of service/glasses were other observed barriers.[37, 45, 46]

Effective efforts to correct those misconceptions, explaining the methods for accessing eye-care services and making these services free of charge

are expected to increase the number of children taken to an eye test, exceeding the current 45% observed in this study. Potential strategies for enhancing parents' knowledge include distributing leaflets, providing online links to vision screening information, and giving out references to pathways for accessing eye-care services.[32] In addition, it is important to advise parents that vision screening is not a comprehensive examination and it is only the first step as certain other conditions may be missed if complete examinations are not performed.[32]

The demographic and socioeconomic factors of the parents significantly influenced their responses, and this has also been supported in previous research.[36] Based on the results reported in this study, educating new parents, easing accessibility to vision screening, making them free of charge, and increasing parental awareness across all working fields, including unemployed parents could increase the number of children being evaluated for vision.[7, 32] Although based on our findings, teachers could be important mediums to refer children for vision screening. Nevertheless, less educated parents and those with or without medical/ocular history should be properly educated about the importance of vision screening for children; education should focus more on providing fathers with more information about the vision of children and informing parents generally about patients' right to avoid/handle potential test refusal.[18, 37, 38, 47]

Currently, no efficient national guidelines were applied to suggest pathways for vision screening, although the Ministry of Health and Education has recently agreed on a newer pathway for vision screening at school reception/year one and another at grade 4. However, the method in which the program would handle the referral for comprehensive eye examinations for children who fail the initial eye test is unclear, which may vary depending on local arrangements in different regions of SA as it was previously suggested in other countries.[32] Moreover, studies have suggested that the most common reason for not undergoing comprehensive eye care after the child fails the initial vision screening was the parents' lack of knowledge about the outcome of the primary screening and/or what it means.[18, 47] Finally, Hartmann et al proposed developing a national integrated data system that would include child-level vision screening data, referral records, and follow-up diagnosis and treatment; following such a route can be very efficient.[48]

This study enrolled 1037 parents, most of whom were mothers (83%). The unbalanced gender recruitment could be a limitation of this study, although mothers may be more attached and closer to children than fathers. The recruited parents were diverse in terms of where they lived, their age, income, education, and the number of children. Furthermore, approximately one-third of the participants did experience some ocular disorders, indicating that they were aware of the importance of vision screening in children. This diversity in response could provide the representation required to reflect the assessment of the targeted population in different regions of the country. The recruitment method used in this study was not typical or similar to other studies that have distributed the questionnaires in hard copies in schools;[32, 33, 45] however, the method in this study avoided possible bias that existed in other studies due to sample selection from a clinically based population.[33] This could be because younger children may not have visited the eye clinic; alternatively, researchers might not have been able to distribute the questionnaires nationwide to have a sample representing the targeted population. That being said, the online survey may have some biases, like including the responses of parents who do not have any children under the age of seven, or parents who may ask for someone's help in responding to these inquiries, so it does not reflect their own thoughts and feelings about the topic. Although, we implanted a question in the survey to verify whether the respondents had children under seven years and excluded some of the collected data as stated in the method section, the responses of some parents who had no children under seven years of age might still have been included. Unfortunately, the second possible bias could not be verified, we were only able to trust the respondents' integrity and voluntary participation stated in their consent.

In summary, this study showed that the majority of parents lack the knowledge about the importance of vision screening and the existing pathways to accessing eye care for young children. It is recommended that parents' awareness of eye-care services be enhanced, and improved communication is needed to educate parents about the importance of vision screening for children, how to access eye-care

services, and share knowledge of the existence of any national/mandatory screening programs. A second recommendation would be developing well-structured protocols to inform parents about their children's vision screening results and provide referral pathways to avoid any dropouts after failing school vision screening. And finally, a national protocol to cover the cost of eye services/glasses may be needed to address those parents who are unable to pay for the cost of eye services.

Acknowledgments

The author extends his appreciation to the College of Applied Medical Sciences Research Center and the Deanship of Scientific Research at King Saud University for funding this research. Furthermore, the author thanks the RSSU at King Saud University for their technical support.

Financial Support and Sponsorship

None.

Conflicts of Interest

The author has no conflicts of interest to declare.

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Original Article

A Survey on Orbital Space-Occupying Lesions during a Twelve-Year Period from a Referral Center in Iran

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Abstract

Purpose: In this study, we describe different orbital space-occupying lesions (SOLs) from a referral center in Iran.
Methods: In this retrospective case series, all records of "orbital tumors" with a definite histopathologic diagnosis at a referral center in Iran were reviewed from April 2008 to May 2020.
Results: A total of 375 orbital SOLs were included. The study population consisted of 212 (56.5%) female and 163 (43.5%) male subjects with overall mean age of 31.09 ± 21.80 years. The most common clinical presentation was proptosis and the superotemporal quadrant was the most frequent site of involvement. Extraconal lesions (276 cases, 73.6%) outnumbered intraconal lesions (99 cases 26.4%). The great majority of SOLs (344, 91.7%) were primary, while 24 (6.4%) were secondary and 7 (1.9%) were metastatic. Benign lesions (309, 82.4%) were much more common than malignant SOLs (66, 17.6%). Overall, dermoid cysts and malignant lymphoma were the most prevalent benign and malignant orbital SOLs, respectively. The malignant to benign lesion ratio was 0.46 in children (≤18 years), 0.81 in middle-aged subjects (19–59 years), and 5.9 in older (≥60 years) cases. The most common type of malignancy was rhabdomyosarcoma in children, lymphoma in middle-aged subjects, and invasive basal cell carcinoma in older age group.
Conclusion: Over the 12-year study period, benign, primary, extraconal orbital SOLs were more frequent than malignant, secondary, and intraconal lesions. The ratio of malignant lesions increased with age in this cohort of patients.

Keywords: Benign Tumor; Extraconal Tumor; Intraconal Tumor; Malignant Tumor; Orbital Tumor

J Ophthalmic Vis Res 2023; 18 (2): 202–211

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Received: 21-05-2022 Accepted: 04-01-2023

Access this article online

Website: https://knepublishing.com/index.php/JOVR

DOI: 10.18502/jovr.v18i2.13187

How to cite this article: Bagheri A, Ashtar-nakhaie P, Aletaha M, Kheiri B, Veisi A. A Survey on Orbital Space-Occupying Lesions during a Twelve-Year Period from a Referral Center in Iran . J Ophthalmic Vis Res 2023;18:202–211.

INTRODUCTION

The orbit is a compact area which is comprised of different tissues including bone, fat, vascular, neural, and muscular components, each of which may be afflicted with various benign and malignant space-occupying lesions (SOLs). SOLs may originate from vestigial tissues or may be the result of invasion from periorbital spaces such as paranasal sinuses, nasal cavity, intracranial space, or even metastasis from distant areas.[1] Orbital SOLs have different presentations ranging from trivial cosmetic issues to loss of sight or even life-threatening conditions.[2]

The frequency of various orbital SOLs varies according to geographic area, ethnicity, age, and sex. This frequency also depends on the department where the study originates from; results from an oculoplastic department may differ from those of a neurosurgery or otolaryngology department.[2–6] Diagnostic criteria are also critical and influence the results of studies; reports based on pathologically confirmed specimens are entirely different from studies that are limited to clinical or radiological diagnoses.[2–7]

Herein we provide data based on histopathologically confirmed orbital SOLs over a 12-year period from an oculoplastic referral hospital in Iran.

METHODS

This retrospective study was based on data from records of patients registered with a general diagnostic code of "orbital tumor" from April 2008 to May 2020 at the Oculoplastic Service of the Ophthalmology Department at Labbafinejad Medical Center. The study was approved by the ethics committees of the Ophthalmic Research Center affiliated with Shahid Beheshti University of Medical Sciences; the approval number was IR.SBMU.ORC.REC.1399.008. The study adhered to the Declaration of Helsinki and informed written consent was obtained from all patients or their guardians prior to surgery.

In all included subjects, orbital SOLs had undergone either incisional or excisional biopsy, and a confirmed histopathologic diagnosis had been established. All cases with unconfirmed pathology were excluded from the study even if a clinical or radiological diagnosis was available.

Demographic data, including age, sex, and laterality of involvement, were determined. Topographic involvement of the orbit was also documented according to results of imaging studies including CT scan and/or MRI. As much as the results of the general physical examinations were documented in the files, these data were also recorded.

Based on definite histopathologic diagnosis, orbital SOLs were classified into seven principal groups including cystic lesions, vascular lesions, neurogenic lesions, inflammatory and lymphoproliferative lesions, mesenchymal lesions, epithelial lacrimal gland lesions, and secondary or metastatic lesions. Notably, inflammatory lesions were included only if they had produced a mass lesion. Lymphoproliferative and inflammatory lesions of the lacrimal gland were tabulated twice: first in the subgroup of inflammatory and lymphoproliferative lesions and a second time under lacrimal gland lesions; however, they were counted only once. We also classified each major group into subgroups, differentiated benign lesions from malignant lesions, and determined the relative frequencies of such lesions according to age.

We used frequency (percentage), mean values, median, and range to describe the data. Statistical analyses were performed using the SPSS software (Version 25.0 Released 2017, IBM SPSS Statistics for Windows, IBM Corp. Armonk, NY, USA).

RESULTS

The study population consisted of 375 patients, including 212 (56.5%) female and 163 (43.5%) male subjects with a mean age of 31.09 ± 21.80 (range: 1–94) years. The mean age was 29.0 ± 20.85 (range: 1–87) years in female patients and 33.9 ± 22.7 (range: 1–94) years in male subjects. We encountered no bilateral involvement in this study, and the right and left sides were almost equally involved. Overall, out of the 375 SOLs, 309 lesions (82.4%) were benign and 66 (17.6%) were malignant; 276 lesions (73.6%) were extraconal while 99 (26.4%) were intraconal; 344 (91.7%) were primary lesions, 24 (6.4%) were secondary, and 7 (1.9%) were metastatic lesions [Table 1].

The number and percentage of patients in major groups with mean age at presentation and gender ratios are summarized in Table 2; corresponding

Table 1. Demographic characteristics of patients and space-occupying lesions.

Specificity	Categories	Patients number (%)
Sex	Female	212 (56.5)
	Male	163 (43.5)
Laterality	Left	190 (50.7)
	Right	185 (49.3)
Position	Extraconal	276 (73.6)
	Intraconal	99 (26.4)
Origination	Primary	344 (91.7)
	Secondary	24(6.4)
	Metastatic	7(1.9)
Pathology	Benign	309 (82.4)
	Malignant	66 (17.6)
Age range (yr)	Children (≤18)	123 (32.8)
	Middle aged (19–59)	209 (55.7)
	Old aged (≥60)	43 (11.5)

Table 2. Major subclassifications of orbital space-occupying lesions in order of their frequencies, together with their age and sex distribution.

Major pathologies	Number (%)	Mean age ± SD	Female/Male
Cystic	138 (36.8)	15.89 ± 14.24	82/56
Vascular	88 (23.5)	35.18 ± 16.79	53/35
Inflammatory and lymphoproliferative	40 (10.7)	45.00 ± 19.38	22/18
Secondary and metastatic	31 (8.2)	60.19 ± 18.79	16/15
Neurogenic	29 (7.7)	36.65 ± 14.77	20/9
Mesenchymal	28 (7.5)	26.29 ± 22.71	13/15
Epithelial lesions of lacrimal gland	21 (5.6)	43.14 ± 20.25	6/15
Total	375 (100)	31.09 ± 21.80	212/163

SD, standard deviation

data for subgroups are presented in Tables 3–9. The most prevalent orbital SOLs, irrespective of benign or malignant nature, are presented in Table 10, and the most prevalent benign and malignant lesions stratified by age are shown in Table 11. The most common category of lesions in this study was cystic lesions and the most common benign lesion was dermoid cyst. The leading malignant lesion was lymphoma, the most common secondary lesion was invasive eyelid basal cell carcinoma (BCC), and the most frequent metastatic lesion originated from breast carcinomas.

We categorized predominant benign and malignant lesions of the orbit according to age at presentation in Table 11. Benign lesions were more prevalent in lower age groups and the frequency of malignant lesions increased with age. The ratio of malignant to benign lesions was 0.46 in children (≤18 years), 0.81 in middle-aged patients (19–59 years), and 5.9 in older individuals (≥60 years).

The site of involvement is presented in Table 12 and demonstrates that the most common site of involvement was the superotemporal quadrant of the orbit. The leading presenting symptoms and

Table 3. Cystic orbital space-occupying lesions.

Cystic lesions	Number of Patients (%)	Percentage of total
Dermoid cyst	113 (82.0)	30.1
Ductul lacrimal gland cyst	7 (5.1)	1.8
Epidermoid cyst	4 (2.9)	1.1
Epithelial cyst (inclusion cyst)	4 (2.9)	1.1
Mucocele	4 (2.9)	1.1
Cystic teratoma	2 (1.4)	<1
Hydatid cyst	2 (1.4)	<1
Hematic cyst	1 (0.7)	<1
Fibroadipose vascular anomaly cyst	1 (0.7)	<1
Total	138 (100)	36.8

Table 4. Vascular orbital space-occupying lesions.

Vascular lesions	Number of patients (%)	Percentage of total
Cavernous hemangioma	66 (75.0)	17.6
Lymphangioma	13(14.9)	3.4
Hemangiopericytoma	4 (4.5)	1.1
Capillary hemangioma	2 (2.3)	<1
Angiosarcoma	1 (1.1)	<1
Angioleiomyoma	1 (1.1)	<1
Arteriovenous malformation	1 (1.1)	<1
Total	88 (100)	23.5

signs are presented in Table 13. Proptosis was the most prevalent symptom in 42.4% of patients, while pain was only present in 3.2% of subjects in the current series.

DISCUSSION

This study evaluated all histopathologically confirmed orbital SOLs over a 12-year period from an oculoplastic referral center in Iran. Generally, there are two types of studies on the epidemiology of orbital SOLs in the medical literature. The first group categorizes the lesions according to the clinical and radiological findings; although such studies may be partly representative, the real findings are not definite. The second group of studies is based on a definite histopathologic diagnosis that suffers from omission of specific lesions which do not regularly undergo biopsy for a diagnosis, such as capillary hemangioma, optic nerve glioma, and meningioma. These second type of reports may also be representative of subjects who require surgical intervention because of functional or cosmetic issues.[6, 8]

Our study showed that the primary lesions were 11.1 times more common than secondary and metastatic lesions. These observations are in line with other large series.[2, 3, 6, 8–10] In our series, benign orbital lesions outnumbered malignant lesions by 4.7 times which is comparable to the report by Kodsi et al,[11] however, in some of the other studies this predominance of benign lesions was less significant,[2, 6, 8, 12] which may be due to the younger age of our study population.

Dermoid cysts were the most common lesions comprising one-third of all lesions in our study,

Table 5. Inflammatory and lymphoproliferative orbital space-occupying lesions.

Inflammatory & lymphoproliferative lesions	Number of patients (%)	Percentage of total
Pseudotumor	17 (42.5)	4.5
Lymphoma	16 (40.0)	4.3
Lymphoid hyperplasia of lacrimal gland	7 (17.5)	1.9
Total	40 (100)	10.7

Table 6. Mesenchymal orbital space-occupying lesions.

Mesenchymal lesions	Number of patients (%)	Percentage of total
Rhabdomyosarcoma	8 (28.6)	2.1
Dermolipoma	7 (25.0)	1.9
Xanthogranuloma	5 (17.9)	1.3
Fibroma	2 (7.1)	<1
Liposarcoma	2 (7.1)	<1
Osteoma	2 (7.1)	<1
Giant cell tumor of bone	1 (3.6)	<1
Chondrosarcoma	1 (3.6)	<1
Total	28 (100)	7.5

which is similar to other large series;[2, 3] however, in the study by Ohtsuka et al, dermoid cysts were the fifth most common tumor.[9] Cavernous hemangioma was the second most common tumor in our series, making up 17.6% of all lesions, which is comparable to some other comprehensive series.[2, 3, 6, 9, 13]

Lymphoma was the most common malignant tumor in our series, comprising 4.3% of all tumors, which is similar to findings by various alternate studies.[7, 14–16] It is notable that the incidence of lymphoma in some developed countries outweighs our rates by two to six times.[4, 5, 9, 17, 18] As an example, in two reports by Shields et al;[3, 6] it was demonstrated that the rate of orbital lymphoma increased from 4% to 8% in the United States after 20 years which may reflect improvements in life expectancy, patient care, and diagnostic capabilities. Moslehi et al[19] and Sjo et al[20] have documented an increase in the incidence of non-Hodgkin lymphoma in orbit and adnexa with increasing age. Our study population was skewed toward younger subjects, and patients older than 60 years comprised only 11.5% of cases which may explain this relatively low rate.

The most common secondary orbital SOL in our report was invasive eyelid BCC which is compatible with the findings by Bonavolonta et al.[2] Kennedy reported orbital invasion by eyelid skin tumors as the second common cause of secondary orbital tumors following invasive tumors from paranasal sinuses.[8] Shields et al, in a report in 1984,[3] noted orbital invasion by eyelid BCC and invasive choroidal melanoma as the most common secondary orbital tumors with an incidence of 3%. In another report by the same group of authors in 2004,[6] invasive BCC ranked fourth with an incidence of only 1% being outnumbered by invasive uveal melanoma and invasive paranasal sinus tumors. Improved care and patient surveillance have probably decreased orbital invasion by eyelid skin malignancies, while more efficacious management for malignant uveal melanoma preserves the eye obviating the need for enucleation and possibly increasing the rate of orbital uveal melanoma. The incidence of orbital invasion by uveal melanoma in our series was only 0.5%. Some older reports from developing areas have revealed that orbital invasion by retinoblastoma accounts for more than half of

Table 7. Neurogenic orbital space-occupying lesions.

Neurogenic lesions	Number of patients (%)	Percentage of total
Meningioma	11 (37.9)	2.9
Schwannoma	9 (31.0)	2.4
Neurofibroma	8 (27.7)	2.1
Glioma	1 (3.4)	<1
Total	29 (100)	7.7

Table 8. Secondary and metastatic orbital space-occupying lesions.

Secondary and metastatic	Number of patients (%)	Percentage of total
BCC from eyelids	11 (35.5)	2.9
SCC from eyelids	5 (16.1)	1.3
Breast carcinoma	3 (9.7)	<1
Choroidal melanoma	2 (6.5)	<1
Sebaceous cell carcinoma	2 (6.5)	<1
Ewing sarcoma	2 (6.5)	<1
SCC from conjunctiva	1 (3.2)	<1
Leukemia	1 (3.2)	<1
Fibrosarcoma from paranasal sinuses	1 (3.2)	<1
Multiple myeloma	1 (3.2)	<1
Melanoma from skin	1 (3.2)	<1
Melanoma from conjunctiva	1 (3.2)	<1
Total	31 (100)	8.2

BCC, basal cell carcinoma; SCC, squamous cell carcinoma

all orbital SOLs in children.[21, 22] In the current series, although 32.8% of all subjects were <18 years of age, we observed no case of orbital invasion by retinoblastoma which may reflect timely diagnosis and treatment of retinoblastoma cases in our population.

Metastatic lesions comprised 1.9% of all orbital SOLs in our study, which is compatible with other studies.[6, 8] In the two studies by Shields et al,[3, 6] the frequency of orbital metastasis increased from 2.5% to 4% over a 20-year period. Similar to our research, some large series on orbital SOLs have revealed breast carcinoma as the most common source of orbital metastasis.[2–4, 6, 23, 24] The two other primary malignancies which may be among the common causes for orbital metastasis are lung and prostate cancers; however, they were not detected in our series.[2–6] It is notable that in various studies from Japan, orbital metastasis from lung carcinoma outnumbered alternative sites of origin.[9, 25]

We observed that the prevalent benign lesion in subjects under 18 years of age was dermoid cyst which accounted for 73 out of 123 cases (59.3%) in this age group, followed by lymphangioma, which involved 10 out of 123 patients (8.1%). This is compatible with multiple prior studies on orbital tumors in children; however, capillary hemangioma was shown to outnumber lymphangioma in these studies as the evaluation was based on clinical data instead of histopathology.[26–28] Orbital malignancies are usually rare in the pediatric age group overall;[26, 27] the most common malignant lesion in this age group was rhabdomyosarcoma which accounted for 8 out of 123 cases (6.5%) and was comparable to previous studies.[2, 26, 28, 29]

The ratio of extraconal to intraconal lesions in our study was 2.8, which is consistent with other

Table 9. Lacrimal gland space-occupying lesions.

Lacrimal gland lesions	Number of patients (%)	Percentage of total
Epithelial lesions 21 (55.3) 5.6		
Pleomorphic adenoma	11 (28.9)	2.9
Adenoid cystic carcinoma	8 (21.1)	2.1
Malignant mixed tumor (pleomorphic adenocarcinoma)	2 (5.3)	<1
Lymphoproliferative lesions	10 (26.3)	2.6
Benign lymphoid hyperplasia	7 (18.4)	1.9
Lymphoma	3 (7.9)	<1
Ductal lacrimal gland cyst	7 (18.4)	1.9
Total	38 (100)	10.1

Table 10. The most prevalent orbital space-occupying lesions.

Orbital lesion	Number	Percentage of total
Dermoid cyst	113	30.1
Cavernous hemangioma	66	17.6
Pseudotumor	17	4.5
Lymphoma	16	4.3
Lymphangioma	13	3.4
Pleomorphic adenoma	11	2.9
BCC from eyelid	11	2.9
Schwannoma	9	2.4
Rhabdomyosarcoma	8	2.1
Total	264	70.2

comparable studies reporting ratios ranging from 2 to 7.[4, 9, 17] The most common topographic area of involvement in our series was the superotemporal quadrant of the orbit comprising about one-third of all cases. This finding is similar to an extensive study by Bonavolonta et al[2] on 2480 patients with orbital tumors. In another study on a population older than 60 years, Demirci et al[5] reported that the area of orbital involvement in 53% of cases was the superior orbit which is consistent with our study despite our younger population of subjects with a mean age of 30 years.

Our series included 38 cases of lacrimal gland lesions comprising 10.1% of all orbital tumors, which is line with previous reports.[2, 31] Epithelial lesions were about twice more common than lymphoproliferative lesions, although these entities are often reported equally.[1] Pleomorphic adenoma and adenoid cystic carcinoma were the most common benign and malignant epithelial tumors of the lacrimal gland which is consistent with previous studies on lacrimal gland tumors.[2, 8, 32] Benign reactive lymphoid hyperplasia and lacrimal gland ductal cyst were the two most common non-epithelial lesions of the lacrimal gland in our study, which differs from many large studies reporting chronic dacryoadenitis as the leading pathology in this category.[3, 6, 8, 33] We observed two cases of malignant mixed tumors, both of which were primary tumors and not the recurrence of pleomorphic adenoma. In most studies, this tumor is reported to be less prevalent than adenoid cystic carcinoma.[2–4, 6] In a review article,[31] the rate of adenoid cystic carcinoma was 3.5 times that of pleomorphic adenocarcinoma.

Table 11. Stratification of the most prevalent benign and malignant orbital space-occupying lesions according to age.

Orbital lesions	≤18 years	19–59 years	≥60 years
Benign (numbers) Dermoid cyst (113)	73	39	1
Cavernous hemangioma (66)	4	56	6
Pseudotumor (17)	3	13	1
Pleomorphic adenoma (11)	1	6	4
Lymphangioma (13)	10	3	0
Schwannoma (9)	2	7	0
Others (80)	19	54	7
309 (82.4% of total)	112 (36.2% of benign)	178 (57.6% of benign)	19 (6.2% of benign)
Malignant (numbers)			
Lymphoma (16)	0	10	6
BCC from eyelids (11)	0	1	10
Rhabdomyosarcoma (8)	8	0	0
Adenoid cystic carcinoma (8)	0	7	1
SCC from eyelids (5)	0	2	3
Breast carcinoma (3)	0	2	1
Others (15)	3	9	3
66 (17.6% of total)	11 (16.7% of malignant)	31 (46.9% of malignant)	24 (36.4% of malignant)

Table 12. Location of orbital space-occupying lesions.

Orbital location	Number of patients	Percentage of total
Superotemporal	123	32.8
Intraconal	99	26.4
Nasal	50	13.3
Diffuse	48	12.8
Superonasal	14	3.7
Inferior	13	3.5
Superior	13	3.5
Temporal	6	1.6
Inferonasal	6	1.6
Inferotemporal	3	0.8
Total	375	100

The most common clinical presentations in our series were proptosis and lump sensation in 42.4% and 31.7% of patients, respectively. This is consistent with a study that recorded clinical findings,[34] although in another study focusing on metastatic lesions, ocular motility problems was a more common symptom than mass effect.[24] Some studies have reported bilaterality in 2–8% of their cases,[5, 17, 25] however we did not encounter any bilateral cases which may be due to the paucity of metastatic lesions in our series.

This study suffers from referral bias and other drawbacks inherent to all retrospective studies. Since only biopsy-proven cases were selected, a small number of familiar entities such as capillary

Table 13. Signs and symptoms of patients.

Symptom or sign	Number of patients	Percentage of total
Proptosis	159	42.4
Lump	119	31.7
Ocular displacement	61	16.2
Ptosis	34	9.1
Lid shape deformity	25	6.7
Conjunctival injection	13	3.5
Pain	12	3.2
Lid retraction	6	1.6
Conjunctival chemosis	6	1.6
Conjunctival mass	5	1.3
Diplopia	5	1.3

hemangioma, optic nerve glioma, and meningioma were recorded.

In summary, at our referral center, 91.7% of orbital SOLs were primary lesions, the most common orbital SOLs were cystic lesions, benign lesions were 4.7 times more common than malignant ones, and extraconal lesions were 2.8 times more common than intraconal lesions.

Acknowledgments

The authors would like to thank Dr. Hossein Salour who introduced and cared for some of the study patients.

Financial Support and Sponsorship

None.

Conflicts of Interest

The authors have no financial interest in the subject of this article.

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Review Article

Pachychoroid Spectrum Disorders: An Updated Review

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Abstract

Pachychoroid disease spectrum is a recent term that has been associated with an increasing number of phenotypes. This review discusses updated findings for each of the typical pachychoroid entities (central serous chorioretinopathy, pachychoroid pigment epitheliopathy, pachychoroid neovasculopathy, polypoidal choroidal vasculopathy, peripapillary pachychoroid syndrome, and focal choroidal excavation), as well as two relatively new additions (peripapillary pachychoroid neovasculopathy and peripheral exudative hemorrhagic chorioretinopathy). Here, we discuss the potential pathogenic mechanisms for these diseases and relevant imaging updates. Finally, we argue for a consistent classification scheme for these entities.

Keywords: Central Serous Chorioretinopathy; Choroid; Pachychoroid; Focal Choroidal Excavation; Pachychoroid Neovasculopathy; Peripapillary Pachychoroid Syndrome; Peripapillary Pachychoroid Neovasculopathy; Polypoidal Choroidal Vasculopathy; Retinopathy

J Ophthalmic Vis Res 2023; 18 (2): 212–229

INTRODUCTION

Pachychoroid is a relatively recent term that has been used to describe a thickened Haller choroidal layer with attenuation of the Sattler and choriocapillaris layers;[1] however, in the near decade since the term's introduction, a universal agreement on its definition has yet to be established. The result of this lack of consensus in defining characteristics has led some authors to combine disease entities while others separate them in their analyses.[2]

Recently, many authors have delineated between pachychoroid and non-pachychoroid forms of pachychoroid disease spectrum (PDS) entities, such as central serous chorioretinopathy (CSCR), pachychoroid neovasculopathy (PNV), and polypoidal choroidal vasculopathy (PCV).[2–6] Notably, Yamashiro et al described that several studies from 2012 to 2018 variably classify PNV ("pachychoroid-driven macular neovascularization without polypoidal lesions") and PCV ("pachychoroid-driven macular neovascularization with polypoidal lesions"); during this period, cases that would classify

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Received: 22-12-2022 Accepted: 12-01-2023

Access this article online

Website: https://knepublishing.com/index.php/JOVR

DOI: 10.18502/jovr.v18i2.13188

How to cite this article: Brown RB, Mohan S, Chhablani J.. Pachychoroid Spectrum Disorders: An Updated Review. J Ophthalmic Vis Res 2023;18:212–229.

as PCV under the current framework were labeled as PNV.[2] Since then, PNV and PCV have tended to be reported as separate entities; however, some authors have continued to include eyes with polypoidal features in PNV.[2] This, therefore, creates issues when reporting imaging findings, treatment outcomes, and clinical management strategies. A detailed discussion of the nomenclature history and issues it has posed can be found in the work by Yamashiro et al.[2] Moving forward, a widespread consensus on the inclusion criteria for pachychoroid spectrum and each pachychoroid entity is paramount to building our understanding of these diseases and their correct pathogenetic mechanism.[1–3] Recently, the following diagnosis criteria has been proposed for pachychoroid: (1) reduced fundus tessellation, (2) pachyvessels, defined as dilated choroidal vessels seen on optical coherence tomography (OCT) or indocyanine green angiography (ICGA), extending the entire length of the vessel to the vortex vein ampullae, causing choriocapillaris and Sattler layer attenuation, (3) a lack of soft-drusen (an exception is made for pachydrusen, which are irregular, scattered yellow–white deposits across the posterior pole), and (4) the presence of CSCR characteristics, such as retinal pigment epithelium (RPE) abnormalities, choroidal vascular hyperpermeability (CVH), or a prior CSCR diagnosis.[2]

This review argues for a more consistent classification scheme for these entities, focusing on the most updated findings for each: CSCR, pachychoroid pigment epitheliopathy (PPE), PNV, PCV, peripapillary pachychoroid syndrome (PPS), and focal choroidal excavation (FCE), as well as newer entities recently added to the spectrum – peripapillary pachychoroid neovasculopathy and peripheral exudative hemorrhagic chorioretinopathy. Further, this review discusses the updated pathogenesis for these entities and attempts to address the debate that these entities exist on a single disease spectrum. Recent imaging analysis will also be discussed.

METHODS

Articles were found by searching online databases for terms such as “pachychoroid” and combinations of the individual entity titles as listed above with “imaging” and “pathogenesis.” Relevant articles published in English language were included in this analysis. Emphasis was given to recently published papers.

RESULTS

Pachychoroid Disease Spectrum Entities

CSCR

Central Serous Chorioretinopathy (CSCR) is the classical pachychoroid spectrum entity with a relatively large body of research; despite this, significant questions remain about its pathogenesis and classification criteria. Compared to other pachychoroid disease spectrum (PDS) phenotypes, CSCR presents in relatively younger patients with serous neurosensory retinal detachment, which may accompany pigment epithelium detachments (PED).[3] As Manayath et al describe, CSCR may also present with posterior choroidal fluid loculations.[7]

Treatment of CSCR depends on disease severity, functional impairment, and patient preference, among other factors. Acute cases are relatively more likely to resolve spontaneously without visual consequence and can be observed.[8] Treatment may be clinically warranted in patients with existing monocular vision, significant symptomatology, or those who desire it.[3] Chronic cases are more likely to require treatment, given their potential to develop neovascular complications, RPE atrophy, or cystoid macular degeneration.[3, 8–10] Patients receiving treatment are more likely to have favorable vision outcomes compared to observation alone.[10, 11] Half-dose Verteporfin Photodynamic Therapy (vPDT) has become a popular treatment choice given its efficacy and improved safety compared to full-dose vPDT.[9, 12] The efficacy of spironolactone and eplerenone in CSCR have also been investigated in randomized control trials, finding mixed results in choroidal thickness reduction and significant change in visual acuity.[13, 14] Recently, Kumar Sahoo et al found that sub-foveal vessels were significantly more likely to respond to PDT, while eplerenone significantly decreased central macular thickness and intraretinal cysts.[10] Through multiple meta-analyses, anti-vascular endothelial growth factor (anti-VEGF) treatments provide no significant improvements in visual acuity in CSCR patients;[15, 16] however, combination therapy

is more useful in the treatment of PDS with neovascular components, such as CSCR with CNV, PNV, and PCV.[3]

PPE

Pachychoroid pigment epitheliopathy has been classified into four types: RPE thickening, hyper-reflective RPE spike, RPE elevation with inter-RPE fissures, and PED.[17] Sakurada et al demonstrated decreased choriocapillaris blood flow in areas coinciding with PPE lesions, suggesting that local ischemia may be the basis of this condition.[18] Similarly, Tagawa et al investigated choriocapillaris flow changes in 32 eyes with PPE compared to 30 healthy controls, finding that eyes with PPE had significantly larger mean total flow void area and average flow void size compared to healthy controls.[19] Further, PPE eyes tended to exhibit a diffuse decrease in choriocapillaris blood flow area, not necessarily spatially related to pachyvessel location. Interestingly, only 21.3% of flow void areas were present over a pachyvessel, leading these authors to suggest that pachyvessel presence does not directly result in choriocapillaris flow deficits.[19] A characteristic case of PPE is shown in Figure 1.

PNV

There has been much debate in the literature regarding the classification and nomenclature of pachychoroid neovascularization (PNV). Previous studies utilized a variety of diagnostic criteria for PNV based on imaging findings, clinical characteristics, and choroidal thickness, among other elements,[20] making comparisons between studies challenging.[2] Such ambiguity in inclusion criteria yielded subjective inclusion of polypoid lesions in PNV studies; accordingly, Yamashiro et al further proposed that moving forward PNV specifically exclude pachychoroid-driven macular neovascularization with polypoidal lesions, as these should tentatively be termed PCV.[2]

Etiologically, PNV joined the pachychoroid spectrum after imaging demonstrated that neovascular lesions spatially correspond to areas with common pachychoroid features, such as thickened choroid, pachyvessels, and increased CVH.[1, 3, 20] Some investigators have suggested that PNV is a late complication of preexisting PPE or chronic CSCR[1]; however, this link is contentious.[21] In support of this theory, previous authors have suggested that given the extensive metabolic demand of photoreceptor cells and relatively limited oxygen supply of the inner retinal vasculature, choroidal thickening decreases diffusion of available oxygen supply from the choriocapillaris to the outer retina, and may therefore lead to VEGF expression from the RPE and subsequent neovascularization.[1] Conversely, others have argued that PNV and PCV occur through mechanisms distinct from the uncomplicated pachychoroid-PPE–CSCR pathway. Demirel et al found that central choroidal thickness (CT) and choroidal vascularity index (CVI) were significantly different between PNV & PCV, PNV & CSCR, and CSCR & PCV, while there was no difference between CT and CVI in PPE & PNV and PPE & CSCR.[21] These authors argued that if PNV and PCV are continuations of the CSCR pathogenesis, these cases should have comparable CVI values to CSCR eyes, rather than the relatively lower CVI reported both in their study and elsewhere in the literature.[21, 22] Although other authors have explained the decreased CVI in PNV by suggesting that anastomoses may relieve choroidal congestion, thereby decreasing choroidal thickness and prompting changes in CVI,[23] the direct link between CSCR-related entities and PNV/PCV has still not been causally related.[21] Further studies elucidating the relationships between these entities are still needed.

In addition, much debate has centered around the involvement of neovascular age-related macular degeneration (nAMD) lesions in PNV classification structures.[2, 24] Some authors have suggested using neovasculature patterns as a differentiation tool.[20] Others have divided PNV cases based on the presence or absence of irregular PED legions.[25] Patients with PNV also tend to be younger and have more RPE abnormalities, thicker choroids, and minimal/absent drusen (excluding pachydrusen) compared to nAMD.[1, 3, 26] A distinction between drusen-driven AMD and PNV has been supported with deep machine learning artificial intelligence[27] and with cluster analysis.[28] Further, the inflammatory cytokine profile in eyes with PNV differs from those with nAMD.[29] Previous studies also suggested eyes with PNV may have lower VEGF concentrations compared to

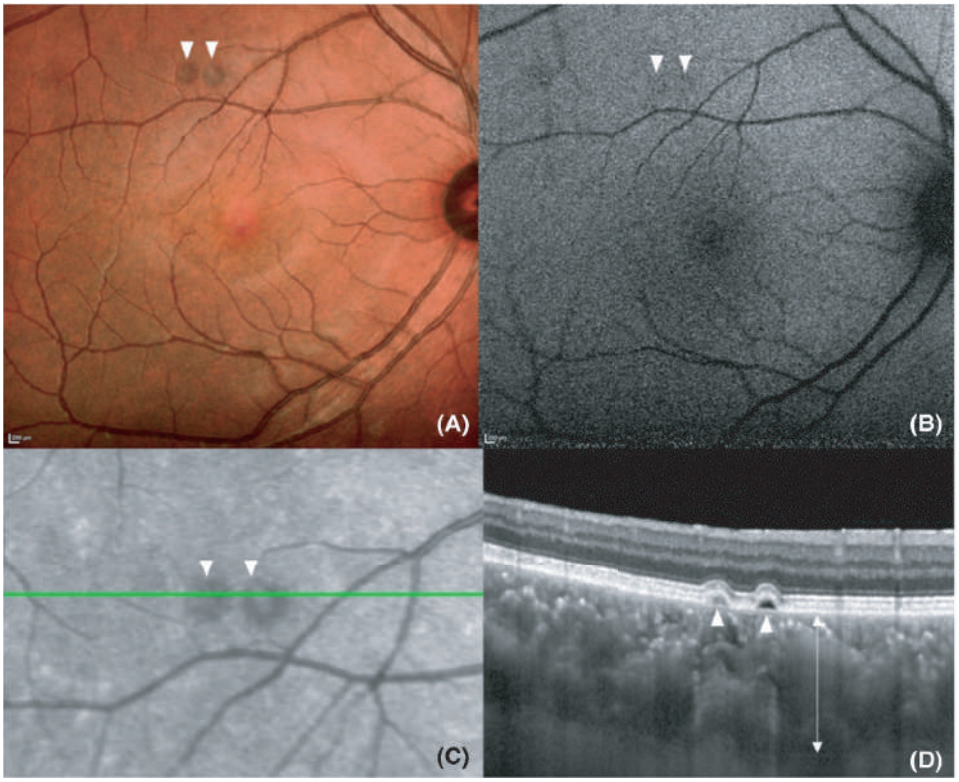

Figure 1. "Imaging of pachychoroid pigment epitheliopathy. (A) Multicolour image highlighting two small PEDs. (B) FAF imaging does not demonstrate major changes in RPE autofluorescence. (C) Near infrared image highlights the position of the line scan for the OCT in image D. Two elevated changes are again seen surrounded by haloes of reduced infrared signal. (D) EDI SD-OCT shows two small serous PEDs (arrowheads) with clear pachychoroid (arrow).
PED, pigment epithelial detachment; FAF, fundus autofluorescence; OCT, optical coherence tomography; EDI SD-OCT enhanced depth imaging spectral domain-OCT" [included with permission from Wiley Publishing].[1]

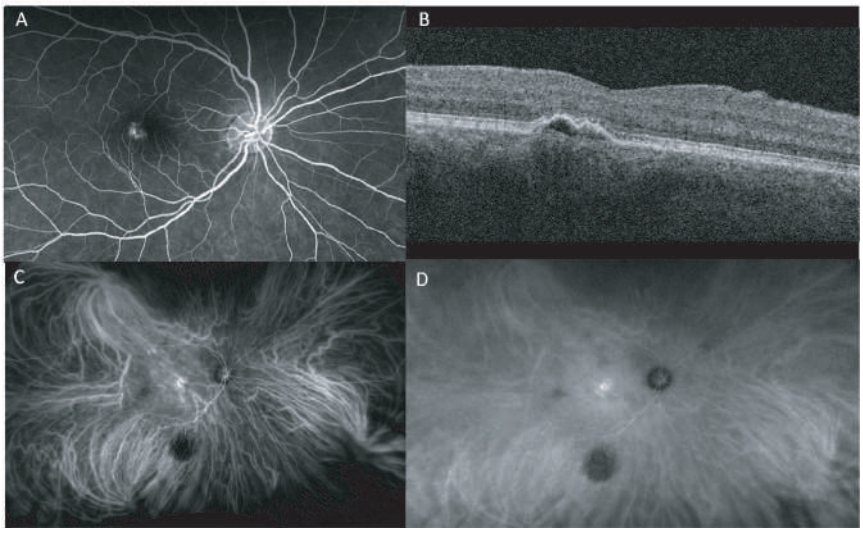

Figure 2. A 58-year-old female with PNV in the right eye. (A) FA demonstrating hyperfluorescence with minimal leakage. (B) OCT showing pigment epithelial detachment (PED) with hyperreflectivity within PED. (C) Early ICG which depicts dilated choroidal vessels and hyperfluorescence. (D) ICG late phase shows diffuse choroidal fluorescence with increasing hyperfluorescence at the lesion site.

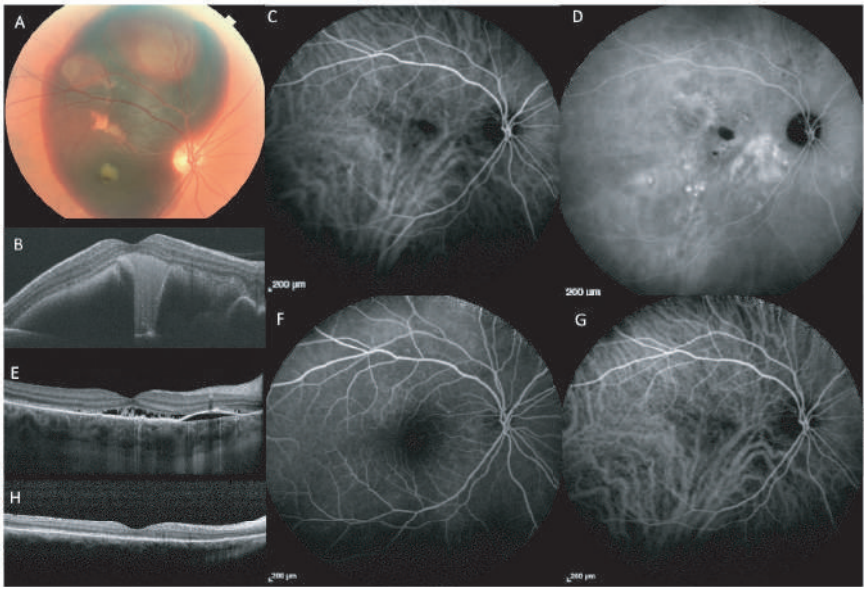

Figure 3. Images of Pachychoroid Choroidal Vasculopathy in a 59-year-old male. (A) Color fundus imaging demonstrating a large, elevated subretinal hemorrhage involving majority of macula and extending to superior mid-periphery. (B) OCT imaging at case presentation. The patient underwent pars-plana vitrectomy, subretinal TPA, SF6, and Aflibercept injection. ICGA post-surgery, early (C) and late (D) stages, showed multiple focal leaks along with polypoidal network. OCT at this stage (E) showed subretinal fluid and pigment epithelial detachment. Subsequently, half-fluence PDT was performed, and complete regression of network was achieved, as shown on early (F) and late (G) phases of ICGA and no activity on OCT (H).

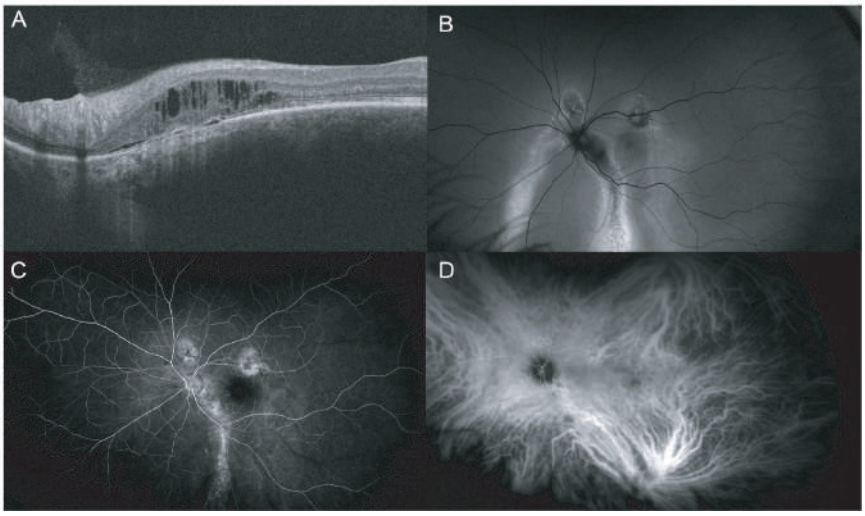

Figure 4. Images of Peripapillary Pachychoroid Syndrome in a 45-year-old male. OCT image (A) demonstrating peripapillary intra-retinal fluid accumulation, with minimal sub-retinal fluid. Fundus autofluorescence (B) shows hyper- and hypoautofluorescence changes along with retinal pigment epithelial tracts. Fluorescein angiography (C), and indocyanine green angiography (D) demonstrate choroidal vascular dilation, along with multiple areas of hyperfluorescence.

nAMD[30]; however, VEGF compartmentalization within the choroid may complicate quantitative measurements.[5, 20]

Advances in imaging techniques are also thought to be important in PNV differentiation [Figure 2]. Pulsation seen in the downstream of the vortex vein on ICGA has recently been proposed as a biomarker for choroidal overload, particularly in eyes with PNV.[31] Conversely, optical coherence tomography angiography (OCTA) has shown a higher sensitivity and specificity than dye angiography in PNV identification.[3, 32]

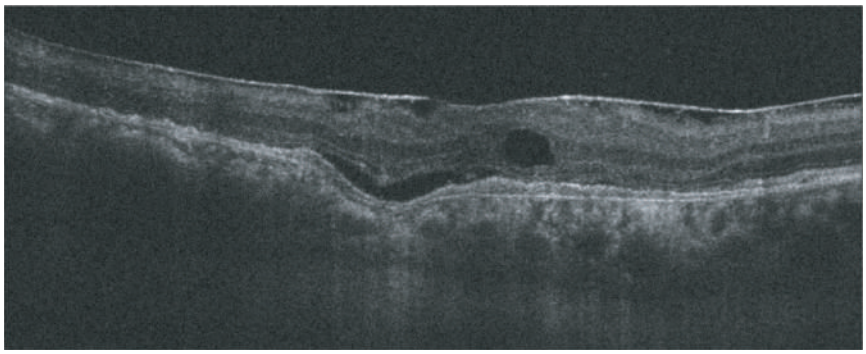

Figure 5. Optical coherence tomography of a 69-year-old male with CSCR demonstrating Focal Choroidal Excavation, along with intra-retinal fluid and an epiretinal membrane.

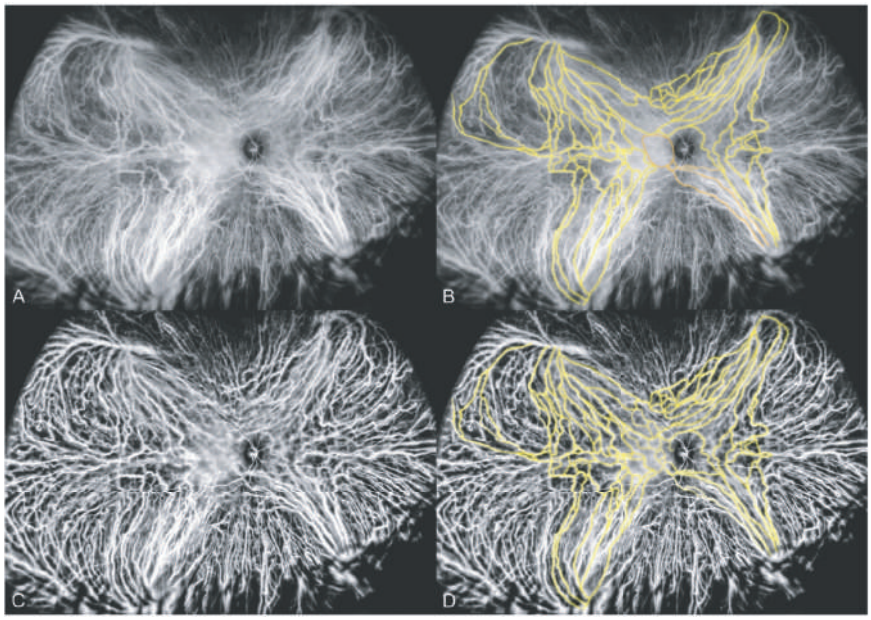

Figure 6. "Wide-field ICG angiogram of a 48-year-old with central serous chorioretinopathy. (A) Image obtained 2:51 min after indocyanine green dye injection. (B) Some of the intervortex venous anastomoses are highlighted in yellow for easier recognition. There are a group of vessels, highlighted in orange, that lead to the inferior macular region and are no longer visible in the central macula because of early leakage (area surrounded by orange outline). (C) Using wavelet contrast enhancement of the middle and low spatial frequency components, haze was removed from the image leaving clear delineation of the larger vessels. (D) The central intervortex venous anastomoses are visible, as highlighted in yellow" [included with permission from Elsevier.][8]

Specifically, cases with type 1 CNV and shallow irregular PEDs are better detected on OCTA imaging,[3, 33] and small PNV lesions with indistinct capillary patterns, fewer core vessels, or absent plaque hypercyanescence are all significantly more likely to be missed by dye angiography.[32] Recently, Sagar et al proposed that SS-OCT may be the most helpful in diagnosing and determining the treatment efficacy.[20] PNV has been shown to exhibit shallow, irregular PEDs on OCT, while the lesions in PCV are sharper and notched.[20] Such irregular PEDs also correspond to the RPE-BM neovascularizations seen on OCTA.[20]

Many treatment options have been explored for PNV; however, differences in case inclusion between studies somewhat cloud this work.[2] Anti-VEGF treatments are equally effective in both PNV and nAMD, but PNV patients often require a longer treatment interval.[3] Aflibercept has proven more effective than ranibizumab at targeting CVH, reducing fluid, and decreasing choroidal thickness.[20, 34, 35] Effects of full-fluence and half-fluence PDT have also been evaluated.[36, 37]

PNV and chronic CSCR have recently been shown to respond differently to half-fluence PDT treatment and may require anti-VEGF + half-fluence PDT combination therapy.[37] Plausibly, PDT monotherapy may successfully treat the CVH component of PNV; however, the neovascular lesions still require an anti-VEGF medication.[36, 37] Monotherapy with anti-VEGF injections[34] or full-fluence PDT,[36] as well as combination therapy,[38] have led to the need for retreatments; however, the lowest recurrence incidence (19%) has been in half-dose PDT combined with aflibercept injections.[39] Overall, the PDT + Anti-VEGF regimens are well tolerated; this combination may result in fewer needed injections and reduce retreatment burden.[1, 38] Future prospective trials are needed to create definitive guidelines surrounding functionally effective treatment modalities for these patients.

PCV/AT1/PAT1

Polypoidal choroid vasculopathy (PCV) has been described as polypoidal vascular dilations overlying a choroidal vascular network.[3] PCV carries many of the same features as PNV, including type 1 (sub-RPE) neovascularization between the RPE-Bruch's membrane junction corresponding to pachyvessel and CVH location.[1, 3] PCV has also been associated with serous or hemorrhagic PEDs near the polypoidal legions [Figure 3] and sub- or intraretinal exudations.[1, 40] Some recent authors suggest that EDI-OCT is crucial in diagnosing this entity, which may demonstrate peaked PEDs containing "thumbprint signs," or rings of hyperreflectivity with hypo-reflective lumens.[41] A "double hump sign" may present where one PED leaks fluid near another PED, while saccular dilations may appear as hyperreflectivity at the RPE level on enface OCT.[41] On imaging, OCTA is more sensitive than ICGA in detecting type 1 macular neovascularization and may help both identify PCV cases and differentiate them from other PDS entities and nAM.[32, 42] Interestingly, the aneurysm-like structures in PCV/AT1 are theorized to result from exposure to pulsatile blood flow,[43] and previous work demonstrated that pulsatile lesions were significantly more likely to be missed on OCTA compared to ICGA.[44]

A wide variety of terms have been used to describe this combination of clinical features and have been reviewed elsewhere.[2, 45] These authors note differences in the frameworks used to classify macular neovascularization, which have compromised the clinical utility of previous works.[2] Recently, aneurysmal type 1 neovascularization (AT1) or pachychoroid aneurysmal type 1 neovascularization (PAT1) have become common in the literature, removing the "polypoidal" terminology to reflect the idea that the lesions are primarily vascular rather than epithelial.[1, 3, 46] A consensus-driven, universal framework is paramount to future studies and our comprehension of the disease. Accordingly, Yamashiro et al recommended that the term PCV should be used cautiously until we have a concreate understanding of the pathogenetic mechanism.[2]

PCV has been proposed to be a common clinical manifestation of several pathogenic processes.[2, 5] PCV and nAMD have similar features;[47] genetic overlap between PCV/AT1/PAT1 and nAMD has been discussed previously.[1, 48] PCV tends to present in younger patients with greater choroidal thickness, CVH, and RPE defects, in comparison to the thinner choroids seen in nAMD.[3] Further, both pachychoroid- and non-pachychoroid-PCV have been discussed.[4, 49] Pachychoroid-PCV and CSCR are more likely to demonstrate diffuse pachyvessels, while in non-pachychoroid-PCV and AMD eyes pachyvessels tend to be focal.[49] Ultimately, Yamashiro et al recommended a framework in which drusen-driven disease entities are classified as nAMD with or without polypoidal lesions, while diseases without drusen are termed "PNV with polypoidal lesions" or "PNV without polypoidal lesions."[2]

Many previous studies do not specify the PCV subtype of their subjects, causing ambiguity when interpreting their results.[5] Pachychoroid-PCV eyes are more likely than non-pachychoroid-PCV to have persistent retinal fluid[4] and chronically increased SFCT after anti-VEGF monotreatment.[6] Further, following anti-VEGF monotherapy, BCVA does not significantly differ from baseline to 60-month follow-up in either group, or between groups.[6] Recently, Vadalà et al evaluated full fluence vPDT + aflibercept in pachychoroid-PCV eyes, finding significant improvement in functional outcomes at 12 months;[5] these findings are similar to those previously reported.[50] Initially treating with vPDT before aflibercept injections has been hypothesized to maintain the effects of initial

vPDT and reduce retreatment in PCV and PNV patients.[5, 38]

Previous authors have speculated that baseline choroidal thickness may be an important predictor for final vision outcomes.[3, 51, 52] Although Chang and Cheng proposed a sub-foveal choroidal thickness (SFCT) threshold of 267.5 μm for anti-VEGF treatment efficacy,[4] the clinical utility of SFCT thresholds is controversial.[53] Patients with PCV may also exhibit significant variability in choroidal thickness,[3, 54] making threshold applications challenging for clinical diagnosis and treatment selection. Further, given the similarity in functional outcomes reported by Shimizu et al,[6] it is unclear if choroidal thickness thresholds will hold significant clinical value in these cases.

PPS

Peripapillary pachychoroid syndrome (PPS) is a relatively new addition to the pachychoroid spectrum, with few cases reported overall.[55] In PPS, patients demonstrate intra or subretinal fluid in the region nasal to the macula and choroidal thickening near the optic disk, rather than the fovea.[3, 56] The disease tends to occur in elderly males[1, 56–59] and may present bilaterally.[3, 56, 60] Patients with this condition may also have other features of PDS, such as CVH, pachyvessels, pigment epitheliopathy, serous PEDs, and hyperfluorescence in the peripapillary region [Figure 4].[3, 41] PPS also exhibits choroidal folds, smaller cup-to-disk ratios, and mild disk leakage on late FA.[41, 56] Recently, Barequet et al described cases of acquired vitelliform lesions in eyes with PPS, a new finding for this disease entity.[59]

The etiology of PPS is still contentious. Some authors have speculated that PPS may have a similar pathogenesis as CSCR, wherein papillary choroidal congestion results in RPE dysfunction and subretinal fluid accumulation.[55, 56] Some have proposed that fluid from the nasal choroid may leak into the retinal space via membrane defects in the external limiting membrane (ELM),[55] while others purport that the peripapillary fluid pocket signifies the fluid entry site from the choroidal vasculature into the retina.[60] Recent evidence has led authors to theorize that anastomotic connections may also play a role in PPS pathogenesis.[43, 55] Peripapillary anastomoses, in combination with the lack of RPE around the optic nerve head, may allow for the direct transmission of choroidal hydrostatic pressure to the inner retinal layers in this region.[57]

Treatment efficacy for PPS varies. Recent cases have resolved spontaneously[55] or with PDT laser.[60] A case of a bilateral PPS, initially treated with dorzolamide eye drops and eplerenone tablets, ultimately achieved retinal fluid resolution and visual acuity improvement after treatment with dexamethasone drops.[60] In both Bouzika cases, visual acuity was significantly affected, making treatment a necessity over the observation only modality suggested by other authors.[55]

The efficacy of anti-VEGF injections is mixed; some have reported favorable outcomes after aflibercept injections,[61] while others reported cases of PPS that were recalcitrant to multiple anti-VEGF medications.[56, 62, 63] Recalcitrant cases have recently shown improved BCVA after low-fluence PDT.[63] Investigations of PDT have also shown long-term significant decreases in both SRF and CSFT,[58] but with complete resolution in fewer patients than seen in CSCR populations.[64] Xu et al investigated long-term treatment outcomes and found that eyes receiving anti-VEGF injections exhibited decreases in choroidal and retinal thickness, but no significant change in best-corrected visual acuity (VA). However, several eyes in this study had remaining SRF which may contribute to the lack of BCVA gain, or had photoreceptor atrophy, which would portend poor vision outcomes regardless of fluid resolution.[57]

Most recently, some reports have documented the potential utility of topical steroids in these cases with good anatomical outcomes.[65, 66] Accordingly, topical steroids can be used as a treatment for fluid resolution PPS; however, because treatment may require extended use and may cause other ocular complications associated with elevated IOP, this modality may be best reserved for recalcitrant cases.

FCE

Focal choroidal excavation (FCE) presents as a choroidal concavity seen on OCT[67] in patients without scleral ectasia, posterior staphyloma, or other scleral abnormalities [Figure 5].[3, 20] Given its choroidal thickening, CVH, and dilated pachyvessels, FCE has been linked with PDS.[68] The place of FCE within the spectrum has not been delineated. FCE coincidence has been

documented in a small percentage of CSCR and PCV/PAT1 cases.[69–71]

Few known risk factors exist; FCE cases have no gender predisposition and affect a wide range of ages.[1, 53, 70] Although FCE usually presents unilaterally and within the fovea, some recent reports suggest it may rarely manifest extrafoveally.[72] FCE is difficult to detect on fundus exam alone but may occasionally present as small yellow lesions and pigmentary changes.[41] EDI-OCT can be useful during diagnosis, as it can demonstrate pachyvessels enlargement, choriocapillaris atrophy, and an intact, depressed RPE.[41] On OCT and ICGA, these cases also tend to demonstrate choroidal attenuation directly below the excavation area corresponding to outer choroidal vessel dilation.[73]

Several classification systems of FCE have been described in the literature. Margolis et al presented "conforming FCE" and "non-conforming FCE," where conforming indicates an intact photoreceptor-RPE junction, while non-conforming signifies a hypo-reflective space between these layers.[74] Later, Shinojima et al proposed three morphological shapes for FCE: bowl, cone, or mixed type, depending on their appearance on OCT.[71] Seemingly, bowl-shaped patterns correlate with more significant atrophic changes and may be associated with a worse prognosis.[71] In a recent study, Capellan et al described three subtypes based on thresholds of central choroidal thickness.[75] These authors found that FCE cases presenting with increased thickness (>200 µm) and cone-shaped morphology were significantly more likely to develop CNV membranes.[75] Finally, the classification structure proposed by Verma et al includes both congenital and acquired FCE, wherein acquired FCE can occur due to a variety of causes, including inflammation, dystrophy, malignancy, or pachychoroid diseases.[67]

Overall, the etiology of FCE is still debated. Some authors have suggested these lesions may arise from a congenital defect in the choroid.[74, 76] Here, the youthful retinal elasticity allows RPE conformity to the area of the predisposing choroidal malformation,[77] further permitting the photoreceptor-RPE junction to remain intact and preventing visual manifestations.[74]With aging, however, decreased elasticity results in layer separation and photoreceptor ischemia, which ultimately cause clinical symptoms and prompt presentation.[67] Other investigators have suggested the disease can also be acquired, with some proposing that inflammation, fibrosis, CNV, or choriocapillaris atrophy may weaken the junction between the RPE and BM, decreasing the overall architectural support and leading to FCE development.[67, 73, 78]

Recently, many authors have discussed inflammatory etiologies of FCE. Verma et al described that hyporeflective spaces between the RPE and photoreceptor layer may also contain hyperreflective elements, potentially indicating residual inflammation or outer segment photoceptor degeneration.[67] Similarly, Ellabban et al suggested that hyperreflective tissue underlying the legion may be evidence of a previous choroidal scar tissue, contraction of which may generate the FCE lesion.[69] Potentially, in cases of severe inflammation, adhesions between the layers may result in a conforming lesion, whereas cases of mild inflammation may result in less adhesion and layer non-conformity.[67] Gan et al found that a majority of FCEs form nearby other comorbid retinal lesions, either at locations within the comorbidity or at its edges, prompting them to suggest that FCEs may occur following other pathologic retinal alterations.[78]

Further, the connection between disease etiology and potential prognosis remains unclear. Verma et al suggested that congenital FCE tended to be static and non-vision threatening, while acquired FCE had the potential to cause complications and vision loss.[67] In 2017, Chung et al noted that lesions tend not to change over time;[68] however, in the study by Gan et al, 22.5% (14 eyes) of eyes with comorbidities experienced a pattern change while 4.8% (three eyes) developed neovascular lesions.[78] If these lesions were acquired secondarily to the underlying disease or clinical treatment, these findings are congruent with Verma et al, who stated that acquired cases tend to have higher complication rates. Large-scale, prospective studies describing the natural course of pachychoroid FCE are needed to validate various classification systems, which may have prognostic value in assessing complication risk and determining clinical follow-up interval.[75] Regular observation is recommended to monitor for treatment-requiring complications, such as neovascularization. To date, no case reports or studies in the literature suggest the need to alter the standard treatment course for the coexisting conditions.[67]

New entities

Recently, several new entities have been proposed to add to the pachychoroid spectrum.

Peripapillary pachychoroid neovasculopathy

Montero Hernandez et al presented a new entity in the pachychoroid spectrum, peripapillary pachychoroid neovasculopathy (PPN), which describes PPS occurring with peripapillary type 1 CNV.[79] Notable findings included: papillonasal pigmentary changes overlying mottled autofluorescence; an irregular PED and pachyvessels on SD-OCT; a large neovascular network and hyper-flow signal on OCTA; and CVH on ICGA. The patient was given treat-and-extend aflibercept, resulting in a good visual and anatomic outcome.[79]

Peripheral exudative hemorrhagic chorioretinopathy

First described by Annesley in 1980, Peripheral exudative hemorrhagic chorioretinopathy (PEHCR) is associated with peripheral subretinal fluid and hemorrhaging, typically located between the ocular equator and ora serrata.[80] Imaging studies have found polypoid lesions in the retinal periphery on ICGA, prompting authors to suggest it is similar to PCV.[81, 82] Schroff et al recently proposed PEHCR as an addition to the pachychoroid spectrum after finding that it was associated with a thickened choroid in the temporal periphery.[80] This pattern of gradually thinning toward the fovea is the inverse of both CSCR [83] and normal eyes,[84] which are thickened subfovealy. This entity has been previously thought to be a variant of AMD;[85] however, AMD demonstrates a relatively thinner retina, leading these authors to suggest it is a separate entity with a different pathogenetic mechanism.[80] Mantel et al described these cases as being self-limiting, with long-term follow-up demonstrating stability, regression, or full resolution.[81] Importantly, given the similarities in their presentation, these lesions must be distinguished from choroidal melanoma which may prevent unneeded radiation or enucleation in these patients.[86]

Pathogenesis

The pathogenetic mechanism of pachychoroid entities is perhaps the most heavily debated component of these conditions. Seemingly, authors agree that uncomplicated pachychoroid, PPE, and CSCR represent stages of a single pathologic entity. However, some disagree that other PDS entities exist on the same linear spectrum.[21] To date, the collective findings suggest that CSCR eyes experience reduced choriocapillaris blood flow spatially corresponding to areas of retinal pigment epithelium ischemia and dysfunction.[87] They propose that the pachyvessel enlargement in eyes with uncomplicated pachychoroid may damage the RPE, leading to PPE, which then becomes CSCR after the RPE damage becomes so significant that it cannot compensate for fluid accumulation and leads to SRF formation.[21]

Generally, authors agree that the fluid in CSCR results from CVH; however, the inciting factors for this CVH are still highly contentious.[8] Importantly, conditions in the PDS spectrum exhibit signs of venous overload,[88] which has been suggested by many as the underlying cause of CVH.[8, 43, 89, 90] Without compensatory lymphatic vessels,[91] the retina relies on the choriocapillaris and RPE to remove excess fluid from the subretinal space; such elevated venous pressure prevents reabsorption and leads to fluid pooling.[8]

Increased venous pressure has been theorized to result from increased blood flow or decreased venous emptying.[8] Some have proposed choroidal arteriovenous malformations or fistulas cause arterial blood to flow directly into a choroidal vein; this increased pressure from arterial blood may cause venous dilation and congestion, leading to pachyvessel formation.[90] In this framework, an anastomotic connection between choroidal arteries and vortex veins results in CSCR, while a connection between a choroidal artery and a choroidopial vein results in PPS.[90]

Separately, increasing evidence has suggested that abnormal venous emptying via vortex vein occlusion may be responsible for choroidal venous congestion and CVH.[43, 92–94] Kishi and Matsumoto described ICGA studies in CSCR eyes which revealed a dilation of the vortex vein ampulla, suggesting an obstruction where the vortex vein transverses the sclera;[43] other authors have hypothesized this site may

hold a valve-like function regulating venous outflow.[8, 94] Further, eyes with CSCR and PNV have increased scleral thickness,[95] which may increase outflow resistance[94] and decrease diffusion permeability,[8] contributing to venous stasis and congestion. In addition, risk factors associated with CSCR development have also been associated with increased scleral thickness. CSCR is more common in middle-aged men,[8] who have a relatively thicker sclera than women.[96] Hyperopic eyes also tend to have thicker anterior sclera, suggesting that axial length may be an intrinsic risk factor for CSCR development.[43, 97, 98] Further studies are needed to understand the contributions of scleral thickness and rigidity to overall vascular resistance.[43]

Vortex vein asymmetry may also contribute to venous congestion in CSCR eyes.[99] Pachyvessels tend to adhere to a specific vortex vein quadrant.[3, 88, 90] Further, PDS eyes demonstrated significant inter-subject variability in the fundal proportion drained by each vortex vein, which was not seen in control eyes.[94] Underdevelopment of one vortex system may represent anatomy predisposed to choroidal venous congestion, overload, and development of PDS.[94]

In addition, venous congestion and stasis have been reported to induce expression of cytokines and other signaling molecules that cause venous dilation and vasculature remodeling.[8] Kishi and Matsumoto suggested that acute venous stasis causes asymmetrical vein engorgement in an area which spatially corresponds to choriocapillaris filling delays; over time, compensatory anastomoses form to relieve chronic venous congestion.[43] Multiple studies have found an association between inter-vortex venous anastomotic connections and pachychoroid entities.[23, 89, 93, 100] Spatially, eyes with CSCR and PNV tended to have anastomoses in the central macula, while eyes with PPS had anastomoses near the optic nerve, providing evidence of a common link between these phenotypes.[89]

Seemingly, these anastomotic vessels have relatively thin walls, making them susceptible to the elevated venous pressure that exists secondary to the venous stasis in these diseases. Dilation of these predisposed vessels were thus purported as the pathogenesis of pachyvessels.[43] Interestingly, as one choroidal system forms a venous anastomosis to relieve congestion and stasis, other authors have suggested that the neighboring system may already have relatively greater venous congestion, thereby, potentiating the venous overload and choriocapillaris leakage.[8] Spaide et al also purported that these dilated anastomoses transmit increased venous pressure to the choriocapillaris, resulting in both leakage and structural damage; therefore, the choriocapillaris attenuation extensively described by previous authors may be due to venous flow abnormalities than mechanical choriocapillaris compression.[8, 89, 92] Further, in some cases, the anastomoses became the prominent vessels within a region, crowding out normal choroidal veins until none remained.[89] Similarly, analyses of the choriocapillaris in eyes with CSCR and PPS found an overall decrease in capillaries, with the ones that remained being longer and wider than normal controls.[8, 92] Chen et al occluded the vortex veins in monkeys, initially noting increased choroidal thickness in the distribution of the occlusion, however, after three months found that non-occluded regions were also thickened, potentially suggesting anastomoses formation resulted in diffuse vortex vein involvement.[101] Overall, it is unclear if vein-to-vein anastomoses occur as a result of venous obstruction, as suggested by Kishi and Matsumoto,[43] or caused by arterio-venous anastomoses, as suggested by Brinks et al.[90] Future studies need to be conducted to delineate if anastomoses are dilations of existing vessels or a neovascular consequence of these pathologies [Figure 6].[8]

Interestingly, Bacci et al found that intervortex venous anastomoses and CVH also occur in healthy eyes, which they attributed to potential subclinical forms of venous insufficiency.[94] Similarly, Jeong et al quantitatively evaluated the choroidal vasculature patients with unilateral CSCR, finding no significant difference in vortex vein engorgement in affected and unaffected eyes, providing further evidence that a predisposition may be present in these patients.[93] Shinojima et al found that 19% of asymptomatic/contralateral eyes of patients with unilateral CSCR ultimately developed a retinal detachment during the follow-up period, further suggesting there may be a predisposing factor.[102] Gerardy et al found that the asymptomatic eyes of unilateral CSCR cases exhibited significantly reduced foveal cone density, suggesting that photoreceptors may be damaged at baseline in a process independent of retinal

detachment; these cones may be particularly sensitive to oxidative stress or abnormal blood flow regulation, which is congruent with findings that CSCR patients exhibit higher levels of oxidative stress biomarkers.[103] Kim et al recently investigated the characteristics surrounding RPE detachment location in CSCR patients.[104] They noted that PEDs closer to the foveal center tended to develop CNV, leading them to hypothesize that the foveal RPE in CSCR patients may be more sensitive to hypoxia, RPE insufficiency, or other tissue stressors.[104]

PPE transitioning to other pachychoroid entities have been reported, including CSCR,[17, 105] PNV,[105] and PCV,[106, 107] which suggests that these entities are related and may be stages of a single disease process.[1, 3] The contralateral, asymptomatic eyes of unilateral CSCR patients have shown signs of PPE in the majority of cases.[105, 108] Similarly, patients with unilateral PCV have also demonstrated signs of PPE in their contralateral eye, all of which became PCV over time.[107] These eyes may have more severe choriocapillaris thinning, leading to further ischemia and RPE disruption.[107, 109] Tang et al further hypothesized that the RPE irregularities seen in PPE represent focal origins to PCV lesions.[107] Eyes with an SFCT of <300 µm may represent very early-stage, compensated PPE.[105]

Recently, authors have suggested that acute and chronic CSCR may have different pathophysiologic mechanisms. Acute CSCR may be due to single anastomosis that spontaneously occludes, prompting fluid resolution, whereas chronic cases may involve multiple anastomoses which involve greater retinal surface area.[90] This hypothesis is congruent with the clinical findings of chronic CSCR appearing as broad and shallow compared to acute cases.[3] Imamura et al previously found that the choroid remains abnormal in eyes with resolved CSCR.[110] Some authors suggest that the dilation and hyperpermeability that accompany venous engorgement are permanent changes to the vasculature, particularly in Haller's layer, creating a predisposition for those with acute CSCR to experience fluid recurrence even after episode resolutions.[8, 20, 43] Chronic CSCR cases have been found to have more hyperpermeable area than acute cases, but without a difference in subfoveal choroidal thickness.[93] Given that patients with acute CSCR have been found to be about 15 years younger than patients with chronic CSCR,[43] some have suggested that older eyes with chronic CSCR may no longer be able to compensate for the fluid overload.[3]

Given the affinity of PDT to target dysfunctional endothelial cells, if aberrant anastomoses are involved in CSCR pathogenesis, this may explain the efficacy of PDT as a treatment modality. Studies have suggested that vPDT may induce choroidal vascular remodeling.[63, 111, 112] By occluding the involved anastomosis, PDT would remove the shunt that is contributing to overload and hyperpermeability.[90] Recent analysis has suggested that although PDT can stop the choroidal leakage, the underlying venous outflow obstruction still remains.[8] Spaide et al discussed surgical decompression of the vortex vein, or the creation of scleral windows to increase scleral outflow; however, the risk profile of PDT likely presents a better option for CSCR patients.[8]

Several extrinsic factors may also contribute to CVH and venous overload, resulting in increased choroidal thickness. Systemic steroid use, "Type A" personality, elevated psychological stress levels, and sympathetic over activity have been previously described as risk factors of CSCR.[113–116] Situations of stress-induced sympathetic response have been hypothesized to increase choroidal blood flow and exacerbate vortex vein stasis.[43] Recently, adrenaline injections in monkeys have shown to cause dilation of the choriocapillaris and choroidal veins.[116] Given these findings, some have suggested that parasympathetic activity may be in some ways protective from CSCR.[117] CSCR eyes have a significant decrease in accommodative ability, which may be linked to a decreased parasympathetic activity in affected eyes.[117] Similarly, pilocarpine, a topical cholinergic, causes choroidal thinning in healthy eyes,[118] while topical atropine, a parasympathetic inhibitor, significantly increases choroidal thickness,[119] providing some support for the hypothesis that sympathetic-parasympathetic dysregulation may lead to a pachychoroid predisposition.[117]

Imaging

Previous reviews have detailed choroidal imaging in eyes with PDS diseases;[1, 41, 53, 87, 120] clinical findings of these entities are presented there in greater detail. In recent years, advances in choroidal imaging technology and post-acquisition

image processing have provided more objective biomarkers for disease identification and treatment efficacy. The focus of this section will be on the utility of parameters and imaging modalities.

Some investigators have argued against absolute quantitative thresholds for choroidal thickness, given that these values may vary with a variety of factors in both diseased and healthy eyes.[3] Choroidal vascular index (CVI), the ratio of vascular lumen to total subfoveal choroid area, has been proposed as a consistent, repeatable measure to monitor disease progression.[121, 122] Recently, cluster analysis was used to determine salient criteria for CSCR or PPE differentiation from healthy eyes.[123] Using an unsupervised machine learning technique, these researchers found that the Haller ratio (Haller layer thickness divided by choroidal thickness), choroidal thickness, and CVI were the most important factors for delineation. The Haller ratio was the most valuable single factor, and, along with total choroidal thickness, it was noted that these two values may be the most useful for clinical practice.[123]

Pachychoroid-related conditions are thought to have differential blood flow between choroidal layers.[87] Blood flow changes precede the retinal changes seen in these diseases, drawing much attention to imaging techniques.[49, 87] EDI-OCT penetrates to the deeper layers of the choroid, allowing for high-resolution imaging and precise quantitative analysis.[87] Further, Swept-Source OCT (SS-OCT) combines the benefit of longer wavelengths (1050 nm) for greater tissue penetration with the rapid capture of numerous images to greatly improve image quality. Averaging multiple images increases in the signal to noise ratio and improves in final image resolution, allowing for both quantitative and qualitative analyses of the choroid.[87] SS-OCTA can also provide clinically relevant information about choriocapillaris flow deficits, as well as identify type 1 and 2 CNV lesions.[87] Variable interscan time analysis (VISTA) has also been combined with SS-OCTA to measure relative blood flow velocity in the choroid, which may be useful in tracking vascular response to treatment over time.[87] Tagawa et al recently demonstrated that choriocapillaris meshwork structure could be visualized *in vivo* by averaging en face OCTA images.[19] Additionally, Doppler imaging has been used to quantify the choriocapillaris and evaluate properties of its blood flow.[87] Future studies utilizing this imaging technique may provide further insight into the various implications of blood flow alterations in these diseases and their respective treatment modalities.

Singh et al further discussed that segmentation slabs on OCT and OCTA machines can help standardize imaging techniques and allows for repeatable choriocapillaris measurements.[87] However, the irregular surface of the inner choroid may cause errors in the automated segmentation process, which may cause inaccurate estimates of flow deficits. Further, RPE atrophy may increase reflectance and cause a mislabeling of normal vessels as CNV.[87] The time involved in manual segmentation or verification is clinically prohibitive.[87]

Although much work has been done to report outcomes from therapies, differences in inclusion criteria and mixed findings between studies indicate the requirement for future works to utilize universal criteria in their analyses to clarify past findings. As we learn more about the disease etiology and increasingly agree on an accurate nomenclature system, additional outcome studies may help evaluate the comparative treatment efficacies within specific subgroups. Additional RCTs with long-term follow-up for pachychoroid-PCV specifically would be helpful in this area.

Summary

Retinal and choroidal imaging have resulted in major changes to our understanding of pachychoroidal disease entities, including potential mechanisms for their pathophysiology and etiology. Advances in imaging techniques are crucial to delineating the differences between the disease entities on this spectrum and provide clarity surrounding the pathogenesis of pachychoroid subtypes, as well as allow for more precise diagnosis and treatment monitoring. A standardized, consensus-based definition of inclusion criteria is needed to effectively compare future findings and correctly categorize pachychoroid entities.

Financial Support and Sponsorship

None.

Conflicts of Interest

None declared.

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Case Report

Inverted ILM Flap Technique in Optic Disc Pit Maculopathy

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Abstract

Purpose: To present the outcome of optic disc pit maculopathy (ODPM) managed successfully with an inverted internal limiting membrane (ILM) flap over the optic disc. A narrative review of ODPM pathogenesis and surgical management techniques are also provided.
Case Report: This prospective interventional case series included three eyes of three adult patients (25–39 years old) with unilateral ODPM and a mean duration of unilaterally decreased visual acuity of 7.33 ± 2.40 months (4–12 months). The pars plana vitrectomy with posterior vitreous detachment induction was performed on eyes, followed by an inverted ILM flap insertion over the optic disc and gas tamponade. Patients were followed for 7–16 weeks postoperatively; best-corrected visual acuity (BCVA) improved dramatically in one patient from 2/200 to 20/25. BCVA in other patients improved two and three lines – to 20/50 and 20/30, respectively. A significant anatomical improvement was achieved in all three eyes, and no complication was detected throughout the follow-up period.
Conclusion: Vitrectomy with inverted ILM flap insertion over the optic disc is safe and can yield favorable anatomical improvement in patients with ODPM.

Keywords: Flap; Internal Limiting Membrane; Macular Schisis; Optic Disc Pit Maculopathy; Optical Coherence Tomography; Serous Macular Detachment

J Ophthalmic Vis Res 2023; 18 (2): 230–239

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Received: Accepted:

Access this article online

Website: https://knepublishing.com/index.php/JOVR

DOI: 10.18502/jovr.v18i2.13189

How to cite this article: Tavallali A, Sadeghi Y, Abtahi S-H, Nouri H, Samadikhadem S, Rezaei M, Mazloumi M. Inverted ILM Flap Technique in Optic Disc Pit Maculopathy . J Ophthalmic Vis Res 2023;18:230–239.

INTRODUCTION

The optic disc pit (ODP) is a rare excavated anomaly of the optic nerve head (ONH), with an estimated prevalence of 2/10,000 and no gender or racial predilection.[1] ODP is most frequently found at the temporal or inferotemporal sections of the ONH, and is assumed as an atypical coloboma of the ONH with dysplastic primitive retinal tissue herniating posteriorly into the subarachnoid space through a defective lamina cribrosa.[2] Mostly, non-complicated ODP are found to be asymptomatic; however, in 25–75% of cases it may develop maculopathy, characterized by cystoid macular changes and/or serous macular detachment.[3] The optic disc pit maculopathy (ODPM) occurs unpredictably and typically in early adulthood, leading to severe visual deterioration, especially in long-standing cases due to the lamellar/full-thickness macular hole development, retinal pigment epithelium (RPE) atrophy, and cystic macular degeneration.[4] Therefore, timely diagnosis and appropriate management of ODPM is necessary. However, given its rarity and controversial pathophysiological aspects, no single treatment is widely accepted and agreed upon as yet.[3] Management strategies mainly include pars plana vitrectomy (PPV) and posterior vitreous detachment (PVD) induction, with or without peripapillary barrier laser photocoagulation, gas tamponade, and internal limiting membrane (ILM) peeling. Recently, covering the ODP using ILM or scleral flaps has been introduced.[4]

Here, we describe three cases of ODPM successfully managed with PPV, PVD induction, insertion of inverted autologous ILM onto the ONH (reverse ILM-flap technique), and gas tamponade with non-expansile concentration (14%) of C3F8 by a single surgeon (AT). We also discussed the current understanding of ODPM pathophysiology and reviewed different treatment strategies described in the literature.

CASE REPORT

Case 1

A 39-year-old white woman was presented with the complaint of progressive decrease of vision in her left eye, which had evolved over the prior six months of presentation. Her best-corrected visual acuity (BCVA) was 20/20 and 2/200 in her right and left eyes, respectively. Funduscopy of the right eye was unremarkable, whereas an ODP at the inferotemporal aspect of the optic disc and cystoid macular edema were revealed in the left eye. An OCT of the left eye showed large, schisis-like cystoid spaces in inner and outer retinal layers, with a large intraretinal cyst underneath a very thin overlying fovea. CMT was 685 µm per structural optical coherence tomography (OCT) scan (Spectralis, Heidelberg Engineering, Inc., Heidelberg, Germany).

Under general anesthesia, a three-port, 23-gauge transconjunctival PPV was performed, followed by induction of PVD. As illustrated in Figure 1, ILM was visualized by membrane-blue-dual dye staining (DORC International, EEC) [Figure 1a]. Then, using a 25gauge+ ILM forceps (Grieshaber advanced DSP tip ILM forceps, Alcon Grieshaber AG, Switzerland), a large ILM flap was peeled from 1 mm temporal to the fovea up to its pedicle at 0.2 mm temporal edge of the ONH [Figures 1b & 1c]. The peeled ILM was then inverted and flattened on the optic disc, covering the pit [Figure 1d]. Finally, fluid-air exchange was performed, and C3F8 14% was injected to stabilize the ILM flap over the ODP. The patient was instructed to remain in a prone position postoperatively. At one-month post-operation follow-up, the BCVA of her left eye was 20/40. Two months after the surgery, BCVA had improved to 20/25. Eventually, intraretinal fluid (IRF) was resolved with only a small amount of residual subfoveal fluid. Remnants of ILM were observed at the disc margin. The mean CMT was reduced to 247 µm . The pre- and postoperative OCT scans of this case are presented in [Figure 2a], and [Figure 2b], respectively.

Case 2

A 27-year-old White man was presented with a one-year history of decreased vision in his right eye; his medical history was otherwise unremarkable. Upon examination, his BCVA was 20/100 in the right eye and 20/20 in the left eye. Funduscopic examination of the left eye was normal; a laterally located ODP and associated macular detachment were noted on the right eye funduscopy. OCT scans of the right eye showed a very high mean CMT of 912 µm, multilayer inner retinal schisis nasal to the fovea, marked IRF in the Henle's layer, and serous neurosensory detachment of the

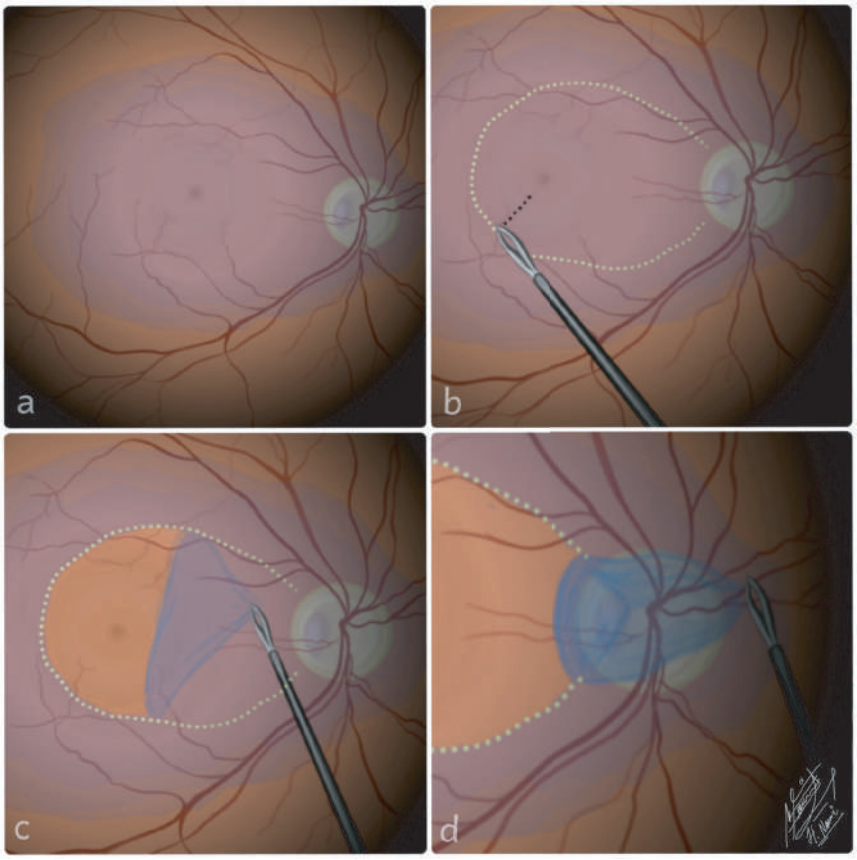

Figure 1. Schematic illustration of the operational technique performed in this study. (a) Membrane-Blue-Dual dye staining was done for internal limiting membrane (ILM) visualization. (b) ILM peeling forceps were used to pinch the ILM at an appropriate position to start peeling, 1 mm temporal to the fovea (black dash line). (c & d) A large ILM flap was peeled up to its pedicles in the optic nerve head adjacency and flattened over the optic disc to cover the pit.

fovea [Figure 3a]. The patient underwent the same procedure as the first case. At the seventh-week follow-up, the macular detachment collapsed, the mean CMT reduced to 367 µm, and significant anatomic restoration was achieved [Figure 3b]; BCVA improved to 20/50.

Case 3

A healthy, White, 25-year-old woman was presented with a history of painless, progressive reduction of central vision in her right eye for four months prior to presentation. The BCVA was 20/70 in the right and 20/20 in the left eye. Funduscopy of the right eye revealed a large inferotemporal ODP and macular edema. In the OCT scan of the right eye, large IRF in the Henle's layer was observed, similar to Case No. 2; the mean CMT was 957 µm [Figure 4a]. The same procedure as described for previous cases was undertaken. Sixteen weeks post operation, her right eye BCVA was 20/30, and retinal edema had significantly resolved. The mean CMT reduced to 330 µm [Figure 4b].

DISCUSSION

Over time, the BCVA of eyes with ODPM can deteriorate to 20/200 or worse in many cases. Notably, spontaneous remission is reported in about 25% of cases.[5, 6] With spontaneous remission, however, cystic changes of RPE and neurosensory retina and lamellar or full-thickness macular holes are likely to develop, with the risk of permanent visual loss;[5] serous macular detachment may also recur.[7] Even in pediatric cases, whose chances for spontaneous resolution are higher,[8] postponing the surgical interventions to monitor the natural course of maculopathy carries the risk of amblyopia development.[9] Hence, primary surgical management of ODPM is

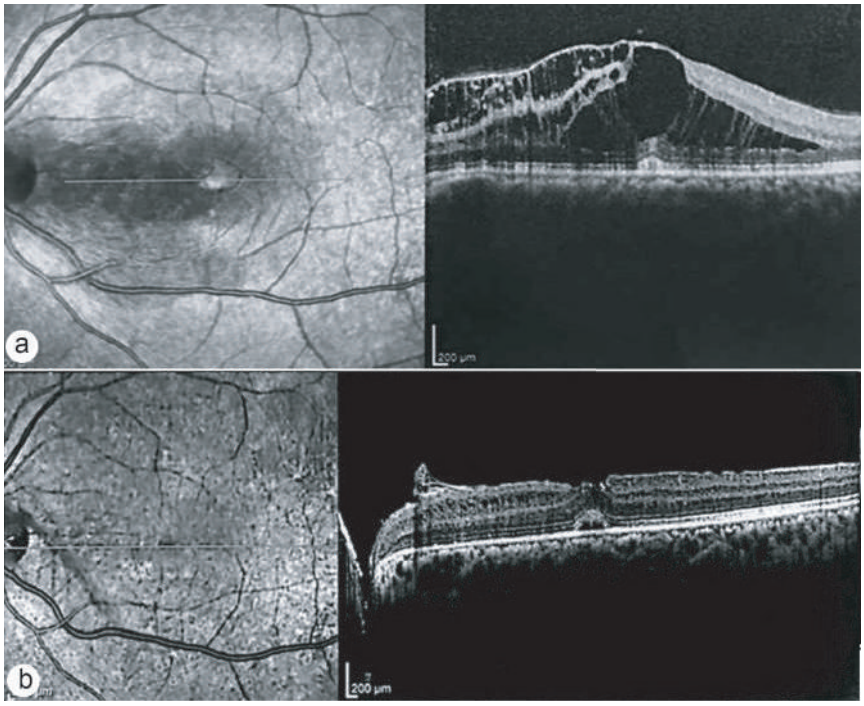

Figure 2. OCT findings in case no 1. (a) Before surgery; schisis-like cystoid spaces in the inner and outer retinal layers and an ample cystoid space in the inner fovea. (b) Twenty weeks postoperatively, ILM remnants appear at the disc margin. Minimal Schises in the inner nuclear layer are noted, and the macula is reattached with small residual sub-foveal fluid.

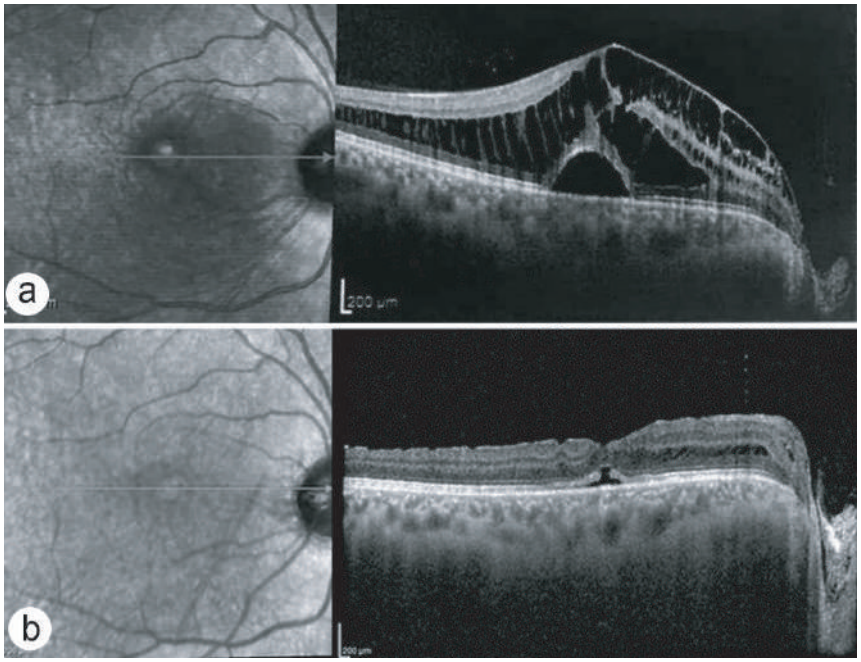

Figure 3. OCT findings in case no 2. (a) Before surgery; note the multilayer inner retinal schisis nasal to the fovea, considerable edema of the Henle's layer, and serous detachment of the macula. (b) Seven weeks post-surgery: Minimal residual fluid beneath the fovea and in the Henle's layer.

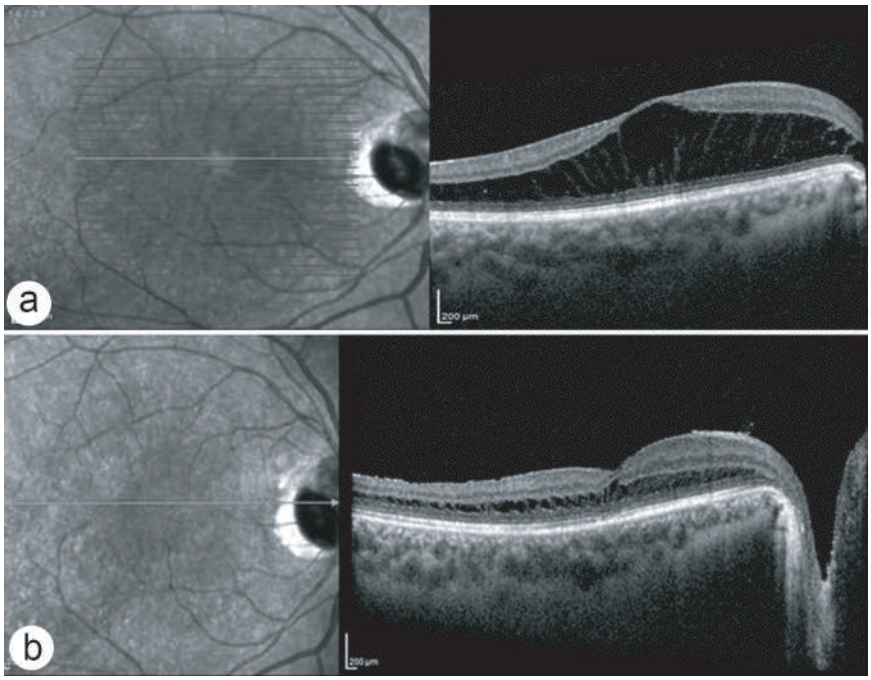

Figure 4. OCT findings in case no 3. (a) Before surgery; huge schisis cavities are visible in the Henle's layer. (b) Sixteen weeks post-surgery: Small residual schisis cavities are left.

recommended, especially in cases with subretinal fluid (SRF) accumulation.[1]

Pathology and Pathogenesis in the Literature

Historically, vitreous has been suggested as the primary source of fluid leakage into the retina through a thin porous membrane constituted of dysplastic retinal tissue covering the ODP.[10] Through serial histopathological sections of electron microscopy, Christoforidis et al could visualize holes in the diaphanous membrane overlying the ODP bridging with a schisis-like cavity in the retina.[11] SRF drainage through pores in the ODP roof was successfully performed by Johnson and Johnson[12] and Postel et al.[13] One hypothesis is that the negative pressure created by posterior hyaloid traction over the porous ODP-covering membrane generates an inward gradient for movement of the liquified vitreous into the retina.[11, 14]

Although inconsistent, vitreous strands over the ONH and peripapillary retina have been detected on OCT scans and electron photomicrographs of patients with ODPM.[2, 14] The role of vitreous traction in ODPM pathogenesis is amply supported by encouraging remission of maculopathy following vitrectomy[15] or spontaneous PVD[16]. Strong vitreoretinal attachment at the disk margin of eyes with ODPM has been reported during surgically induced vitreous detachment.[7] In addition to the role of posterior hyaloid traction, the tangential traction on the retina caused by ILM is also proposed to exert elevational traction on the retina, maintaining the inward fluid gradient into the retina (via ODP).[17] Post-vitrectomy subretinal migration of gas and silicone oil further supports communication between vitreous cavity and subretinal space through ODP; curiously, it happens when no vitreoretinal traction exists, indicating the involvement of other pathogenic mechanisms.[12]

Cerebrospinal fluid (CSF) oozing from the adjacent subarachnoid space is the second plausible fluid source; it was first proposed in 1964[18] after Regenbogen et al noticed a pulsating transparent membrane over the ODP during surgery, which they attributed to CSF pressure fluctuations. Akiba et al had a similar observation, which they ascribed to intravitreal traction caused by anomalous Cloquet's canal.[19] Friberg et al reported free pulsation of glial and vitreous remnants overlying ONH into and out of ODP in an eye with visible PVD.[20] They also recognized a retrobulbar cyst communicating with the vitreous cavity through B-scan ultrasonography

and documented a constant relative hypotony in the affected eye, presumably due to intraocular fluid drainage into the cyst and, ultimately, the subarachnoid space.[20] In 2006, intracranial migration of silicone oil was noted on brain magnetic resonance imaging scans of a patient with ODPM presented with a headache after vitrectomy and silicone oil injection.[21] The direct communication of intraretinal cystoid spaces and the lamina cribrosa gap in the ODP[22] and their connectivity with the vitreous cavity was later visualized using high-resolution, enhanced depth imaging (EDI), and swept-source (SS) OCT scans.[23––25] As theorized by Johnson and Johnson,[12] anomalous interconnection and fluctuation of the pressure gradient between intra- and extra-ocular spaces enable CSF and vitreous aqua to move through the ODP. When intracranial pressure (ICP) decreases, the syneretic vitreous is sucked toward the communicating perineural space, and then with a rise in pressure, trapped vitreous and/or CSF is ejected into/under the adjacent retina and posterior vitreous cavity. The same mechanism could explain subretinal migration of gas and oil, post-vitrectomy, and the occurrence of maculopathy in pediatric ages when liquified vitreous is uncommon.[12]

Regarding the morphology and progression of ODPM, Lincoff et al[26] first introduced the so-called bilaminar retinoschisis concept, in which liquid accumulation emanates from the inner neurosensory retina, extending outward through outer layer lamellar holes. They proposed that true serous macular detachment occurs merely as a complication of longstanding intraretinal edema. Although this view has been widely accepted,[23] it has been challenged by occasional observations of an outer layer hole in OCT scans[27, 28] and cases of ODPM with macular detachment, where no inner retinal schisis-like cavity was found.[29] Todorich et al reported a case of ODPM with a direct connection of SRF to ODP, as detected on spectral-domain (SD)-OCT scans.[30] Using high-resolution OCT, Imamura et al showed that fluid could move straight from the ODP to multiple retinal layers, including the sub-ILM space, ganglion cell layer, inner and outer nuclear layers, and subretinal space.[28] The outer nuclear layer is usually affected – as seen in our cases; one interpretation could be that in the majority of cases, the inner retina and/or subretinal space are involved secondarily to an initial passage of fluid through the outer retina.[31] Intriguingly, Skaat et al described two distinct OCT patterns in their cases: (i) A predominant serous detachment pattern, with no to minimal schisis-changes of the photoreceptor layer in pediatric patients (mean age: 9 years old). (ii) A multilayer schisis pattern in older adults (mean age: 31.7 years old).[32] The former pattern in younger patients has been reported by others as well, but it was not confined to the pediatric population.[33] Although direct SRF conduit from ODP is rare,[1] perhaps when present, it allows fluid to pass beneath the retina much sooner than expected for conversion of asymptomatic ODP to ODPM in early adulthood. ODPM does occur unpredictably; however, blunt ocular and head trauma has been suggested as a potential trigger, especially in pediatric-onset cases. Rii et al have attributed this to the severe hyaloid face adhesion in pediatric patients exerting an anteroposterior tractional pull on the macula following trauma.[34] Another explanation could be the sudden rise in ICP after trauma, forcing CSF into/under the retina.[3]

Nevertheless, both vitreous and CSF could serve as the pathogenic source of the accumulated fluid, passing into the retina through multiple layers, most commonly the outer nuclear layer.[11] Moreover, both vitreoretinal traction and ICP pressure fluctuation play a role in the pathogenesis of the disease, either being prominent at certain ages and/or under different circumstances. We also suggest that a direct subretinal connection with the ODP cavity together with a traumatic experience may act as risk factors for accelerated progression toward ODPM in cases with asymptomatic ODP.

Surgical Techniques in the Literature

As previously mentioned, tractional forces over the ONH allow for fluid entrance through the ODP, and the traction exerted upon the peripapillary and macular area could promote schisis separation of retinal layers, facilitating fluid migration into the retina. Therefore, complete vitrectomy with PVD induction is the mainstay of ODPM treatment.[3, 27] Hirakata et al showed that although, it took up to a year for the attachment to occur, the complete retinal attachment in seven of the eight eyes were achieved with isolated PPV and PVD induction.[35] An alternative surgical approach is placing scleral buckles between the optic disc and macula, with a similar success rate of 85% as PPV and PVD induction. Besides alleviating vitreoretinal traction,

scleral buckling is suggested to obstruct the fluid passage from ODP.[36] However, this tricky technique is rarely applied in the management of ODPM.[4]

ILM peeling, gas tamponade, and juxtapapillary endolaser photocoagulation are commonly utilized adjunctive procedures alongside PPV. The rationale behind these procedures and their additional benefit to vitrectomy is still controversial. Pneumatic retinopexy alleviates vitreomacular traction by inducing PVD and displacing accumulated fluid;[37] however, when applied without PPV, it has a temporary effect[38] and a retinal reattachment rate of 50% with a mean number of 1.8 injections.[39] Laser application is tentatively proposed to seal the route of the ODP to the fovea, but it has a very low success rate,[40] probably because choroid and deep retinal layers absorb much of the laser energy. It also bears the risk of causing significant visual field defects.[41] While re-intervention was needed in 40% of the cases, combined gas tamponade and laser application had a 75% success rate.[42] After unsuccessful photocoagulation or pneumatic retinopexy, PPV and fluid air exchange, with or without laser treatment, have yielded an 88% reattachment rate.[6] More recently, ILM peeling has been suggested to ensure the removal of all anteroposterior and surface-parallel traction forces from the retina.[43] Three multicenter studies evaluated the surgical success rates gained with PPV and PVD induction +/– ILM peeling, gas tamponade, and juxtapapillary endolaser and evaluated the extra therapeutic gain associated with each of these adjunctive treatments[1, 15, 44] They showed an overall 75–86% retinal attachment success rate, but no significant improvement gained with ILM peeling or temporal laser application was found; only gas tamponade showed additional efficiency in the study by Avci et al;[44] however, all these studies suffer from small sample sizes and heterogeneities in the surgical procedures employed.[1]

Marticorena et al reported a case successfully treated with peeling of ILM after an initial failure of PVD and laser application[45] PVD induction, gas tamponade, and ILM peeling resulted in favorable outcomes in three ODPM cases within a few months, as described by Georgalas et al.[46] In a retrospective analysis of five patients who underwent PPV plus gas injection with or without ILM peeling, Skaat et al reported complete SRF resolution in the former group whereas macular detachment persisted in patients for whom ILM peeling was not performed.[32] Even considering the different clinical and morphological characteristics of the two groups, it could still be inferred that ILM peeling is a critical surgical maneuver to alleviate maculopathy. Despite the formation of macular holes in 57% of the eyes operated, Shukla et al achieved excellent results with vitrectomy, ILM peeling, and gas tamponing in seven cases. Three out of four holes were closed spontaneously, and the final visual outcome was unaffected by macular hole development during the recovery course.[43] Although fovea-sparing ILM peeling has been suggested to minimize the risk of macular hole formation,[47] leaving a central island of ILM on the macula showed no protection against macular hole formation in one out of two eyes that underwent the procedure.[43] Moreover, full-thickness macular hole formation has been reported following PVD, gas tamponade, and laser photocoagulation without ILM peeling;[48] as Shukla et al proposed, most of the risk could be attributed to removing the strongly adherent posterior hyaloid face.[43]

Spaide et al introduced another adjunctive maneuver beside PPV, that is, partial-thickness fenestration of the retina, radial to ONH. It is proposed to allow fluid redirection toward the vitreous cavity instead of the intra-/sub-retinal layers.[49] They later achieved 94% foveal fluid resolution with this technique.[50] However, a previous attempt to create a fenestration connected to schisis cavities by Slocumb and Johnson resulted in persistent macular detachment due to premature closure of the fenestration soon after surgery.[51] Moreover, this technique will not be effective in the presence of a direct conduit beneath the retina.

Sealing the congenital pit with platelet-rich plasma (PRP) or fibrin glue has shown promising results and seems to shorten the long duration of restoration following surgery.[30, 52] However, the plugs are temporary and cannot be regarded as a permanent solution. The long-term safety of PRP is unknown as it can theoretically trigger proliferative vitreoretinopathy.[30] The use of fibrin glue carries the risk of allergic reactions and microbial transmission.[53]

Insertion of an inverted ILM flap over the ODP has recently been suggested; the flap could act as a physiologic physical barrier against

vitreous and oil migration and induce gliosis and cell proliferation within the ODP cavity.[54] Two months after complete PVD induction, ILM peeling, reverse ILM flap insertion, and gas tamponing, pit remodeling and partial closure were observed. We did not detect any macular hole formation in the three operated eyes, which was consistent with previous case reports using this technique.[55, 56] However, a limitation of our study should be taken into account in this regard, that is, the follow-up periods were relatively short and heterogeneous in length. Nevertheless, following a similar rationale to that of the ILM flap procedure, autologous scleral flap transplantation has also been proposed[57] but has an inherent risk of optic nerve damage.[58] Babu et al retrospectively compared the treatment outcomes associated with PPV+ILM peeling alone (group 1, *n* = 8), +ILM flap (group 2, *n* = 7), or +scleral flap (group 3, *n* = 8); covering of the ODP with either flap resulted in better anatomical outcomes than PPV+ILM peeling alone, and no significant difference was observed between groups 2 and 3 in terms of final anatomical results (anatomical success rates: 25% in group 1, 85.7% in group 2, and 87.5% in group 3; *P* = 0.019).[59] Results from a preliminary prospective study of nine eyes undergoing PPV + translocation of an ILM flap/transplantation of an inverted ILM flap were also indicative of favorable anatomical and functional outcomes (mean pre- and postoperative CMTs: 723.4 and 398.1 microns; reattachment rate at the last follow-up: 56% [5/9]; the mean BCVA improvement corresponded to three lines of visual improvement). Treatment outcomes were comparable with either method of ILM flap covering over the ODP.[60]

In conclusion, surgical intervention is crucial in the management of OPDM. In addition to removing the traction over the ODP, the elevating stress over the retina and the risk of schisis formation should be minimized through PVD induction and ILM peeling, allowing retinal layers to reattach over time. However, in the presence of communicating fluid sources, the restoration process is generally slow because intermittent pressure gradients caused by fluctuations in CSF pressure could still push fluid into the retina. More recently, covering the congenital pit with an ILM flap was suggested. In our experience, the inverted ILM flap procedure is efficacious and safe in the management of ODPM. This procedure resulted in substantial functional and anatomical restoration in our three cases; eyes remained complication-free during the 7–16 weeks of follow-up. This emerging surgical technique invokes cellular proliferation and tissue construction inside the ODP and closes the communicating cavity, substantially facilitating remission. Gas tamponade may further facilitate fluid egression from the retina and keep ILM over the ODP long enough to induce and maintain cellular growth and tissue remodeling inside the pit.

Ethical Considerations

The protocol of the present study was approved by the local ethics committee; the study adhered to the principles of the Helsinki declaration. Informed consent was obtained from all participants.

After briefing participants on the content prepared for publication, signed informed consent letters were obtained.

Declaration of Patients Consent

The authors certify that they have obtained all appropriate patients consent forms. In the form the patients have given their consent for his images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identities, but anonymity cannot be guaranteed.

Financial Support and Sponsorship

This study received no funding.

Conflicts of Interest

The authors declare that they have no significant competing financial, professional, or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

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Case Report

Posterior Microphthalmos Pigmentary Retinopathy Syndrome

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Abstract

Purpose: To report a case of a rare disease entity Posterior Microphthalmos Pigmentary Retinopathy Syndrome (PMPRS) in a 47-year-old female with a brief review of literature.
Case Report: A 47-year-old woman presented with a history of defective vision with an associated difficulty in night vision. Clinical workup was done, which included a thorough ocular examination showing diffuse pigmentary mottling of fundus, ocular biometry showing short axial length with normal anterior segment dimensions, electroretinography showing extinguished response, optical coherence tomography showing foveoschisis, and ultrasonography showing thickened sclera–choroidal complex. Findings were consistent with those reported by other authors with PMPRS.
Conclusion: Posterior microphthalmia with or without other ocular and systemic associations should be suspected in cases with high hyperopia. It is mandatory to carefully examine the patient at presentation and close follow-ups are needed to maintain visual function.

Keywords: Foveoschisis; *MFRP* Gene; Microphthalmos; Posterior Microphthalmos; Retinitis Pigmentosa

J Ophthalmic Vis Res 2023; 18 (2): 240–244

INTRODUCTION

Microphthalmia is a condition characterized by axial length (AXL) of the eye being less than two standard deviations with the normal for that age.[1] It can be simple, presenting as an isolated entity or complex, associated with other malformations. Furthermore, it can also be sub-classified as nanophthalmos, anterior microphthalmos, and posterior microphthalmos. Nanophthalmos or simple microphthalmos is a condition wherein the AXL is short due to both small anterior and posterior segments.

Posterior microphthalmia (PM), first termed by Spitznas et al[2] is a rare entity characterized by shorter AXL with smaller posterior segment dimensions in association with sclero-choroidal thickening and normal anterior segment. Although majority of PM cases have been reported as sporadic, an autosomal recessive form of inheritance is proposed for familial cases. Few

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Received: 05-08-2020 Accepted: 15-12-2021

Access this article online

Website: https://knepublishing.com/index.php/JOVR

DOI: 10.18502/jovr.v18i2.13190

How to cite this article: Adeel SS, KA SM, Sharma A, Shah VJ, Shetty A. Posterior Microphthalmos Pigmentary Retinopathy Syndrome. J Ophthalmic Vis Res 2023;18:240–244.

case reports have documented an association with uveal effusion syndrome,[3] pigmentary retinopathy, foveoschisis, papillo-macular retinal folds,[2] macular hole,[4] and retinal dialysis[5] amongst other conditions.

A few reports of a new syndrome called Posterior Microphthalmos Pigmentary Retinopathy Syndrome (PMPRS) characterized by PM, foveoschisis, retinitis pigmentosa, and optic disc drusen have been recently described. Literature on this new entity is however sparse with the largest reported case series of five family members by Morillo Sánchez et al[6] in 2019. Mukhopadhyay et al[7] in 2010 described three novel mutations in the gene related to this syndrome in seven individuals from four families; they called the ocular condition as Membrane type Frizzled-Related Protein (*MFRP*)-related oculopathy.

CASE REPORT

A 47-year-old female presented with a history of defective vision in both eyes for many years with an associated difficulty in night vision. She also had a history of using thick glasses since childhood with unremarkable past medical history. She was born from a non-consanguineous marriage and had no systemic illness at presentation. There was no history of any ocular trauma, ocular surgery, or a history of visual dysfunction in her family.

On ocular examination, the visual acuity in the right eye (OD) was 0.25 and 0.16 in the left eye (OS) with a subjective cycloplegic refraction of +10 D. Intra-ocular pressure was 13 mmHg in OD and 12 mmHg in OS as measured by Goldmann Applanation Tonometry. On Slit-lamp examination, her anterior segment was unremarkable with a normal anterior chamber depth (ACD). Vitreous evaluation showed presence of pigmented cells in both eyes. Fundus examination revealed diffuse pigmentary changes characterized by pigment clumps and bone spicule pigmentation of mid-peripheral and peripheral retina, waxy pallor of disc, vascular attenuation, and blunting of the macular reflex [Figures 1a & 1b]. Ultrasound B-scan of both eyes was suggestive of a short AXL and sclero-choroidal thickening [Figure 2]. On ocular biometry, the AXL was 18.37 mm in OD and 18.00 mm in OS, the white-to-white (WTW) corneal measurements were 12.0 mm OD and 12.4 mm OS, and the ACD was 3.52 mm OD and 3.36 mm OS [Table 1]. Optical coherence tomography passing through the fovea showed foveoschisis in both the eyes [Figure 3]. Furthermore, ERG showed extinguished wave response in both the eyes [Figure 4]. She was explained the prognosis and was advised low vision aid for rehabilitation. Although PMPRS is a phenotypic diagnosis, we asked the patient for a genetic workup so as to identify the causative gene. However, the patient denied further investigations in this regard as it did not alter her visual prognosis or treatment outcome.

DISCUSSION

Buys et al[8] in 1999 were the first to report a 68-year-old male patient with a combination of retinitis pigmentosa, nanophthalmos, and optic nerve head drusen. They hypothesized that the retinal pigmentation was due to chronic serous retinal detachments and choroidal detachments.

Ayala-Ramirez et al[9] in 2006 described in four siblings of a Mexican family the ophthalmic features of retinitis pigmentosa, foveoschisis, posterior microphthalmos, and optic disc drusen and proposed this disease entity as a new oculo-genetic syndrome. They also described clinical criteria for the diagnosis of this syndrome.

In 2008, similar findings were noted by Crespi et al[10] in a Spanish family with three affected brothers. The authors put forth this disease as a distinct autosomal recessive entity caused by a novel frame-shift mutation in the membrane type frizzled-related protein (*MFRP*) gene. Mutations in the 13-exon *MFRP* gene located on chromosome 11q23 encoding a trans membrane protein with 579 amino acid residues was demonstrated to be present[7, 9, 10] in prior case reports on PMPRS. Predominantly, it is expressed in ciliary epithelium and the retinal pigment epithelium.

Similarly, our patient had PM with normal anterior segment dimensions. The antero–posterior diameter was 18.7 mm (OD)/18.0 mm (OS), with a hyperopia of +10 D (OU). We found optic disc pallor, diffuse pigmentary changes, vascular attenuation, blunting of the macular reflex, and extinguished ERG response meeting the criteria proposed by Ayala Ramirez et al.[9] However, unlike Ayala Ramirezetal, there was no evidence of optic nerve head drusen and papillo-macular folds.

Pehere et al[11] reported two siblings with PMPRS syndrome and postulated autosomal recessive

Table 1. Ocular biometric measurements of both eyes of the patient.

Eye	Axial length (mm)	White to White (mm)	Anterior chamber depth (mm)
Right	18.37	12.00	3.52
Left	18.00	12.40	3.36

mm, millimeter

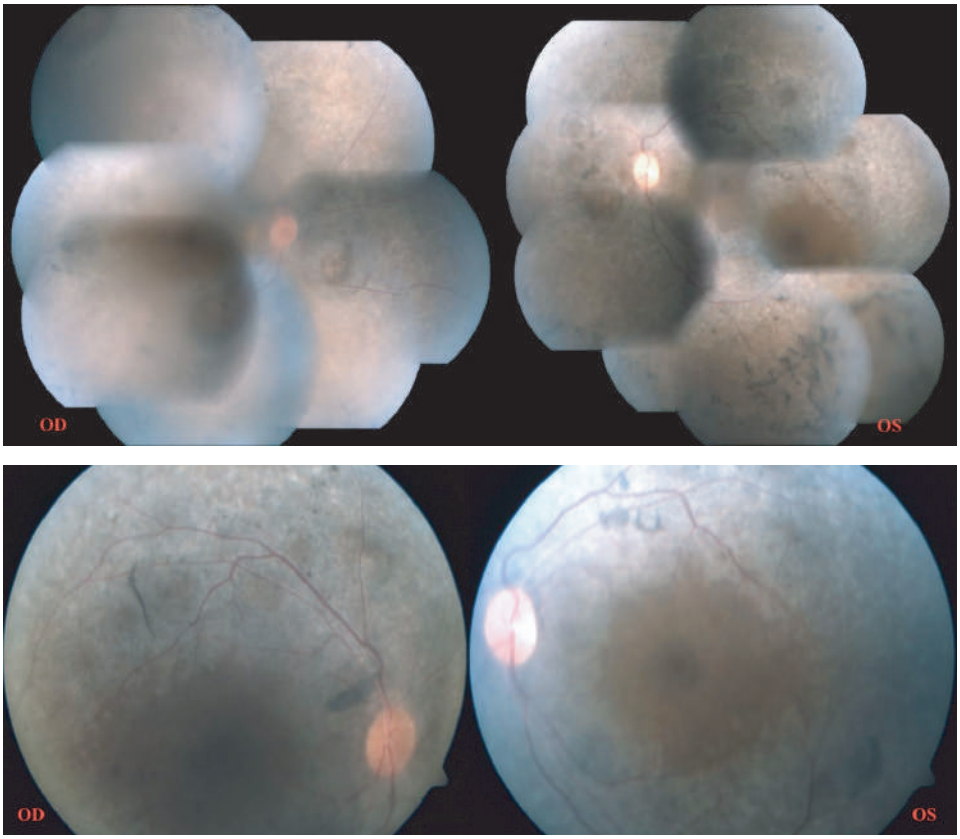

Figure 1. Fundus photograph of the posterior pole of both eyes showing disc pallor, more appreciated in the left eye, pigmentary mottling, and vascular attenuation. **(b)** Fundus montage of both eyes showing pigment clumps and bony spicule pigmentation in mid-peripheral and peripheral retina.

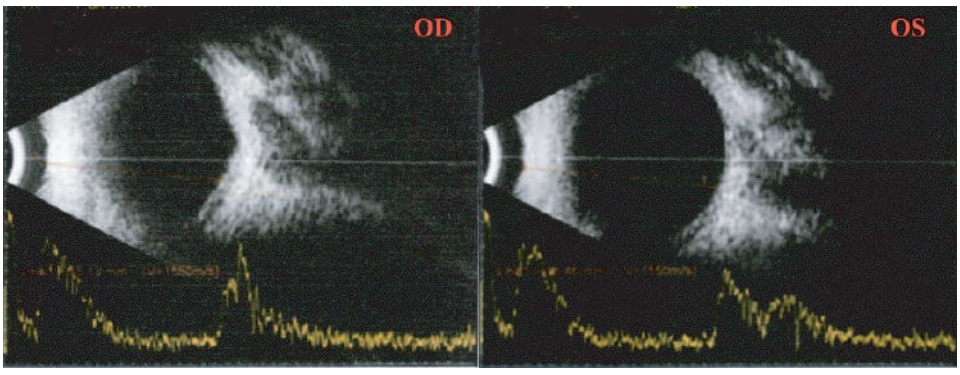

Figure 2. Ultrasound B-scan of both the eyes showing a short axial length with associated sclero-choroidal thickening in the para-papillary area.

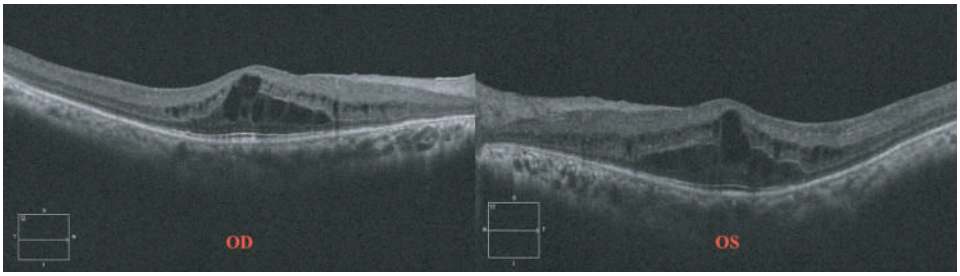

Figure 3. Optical coherence tomography of macula passing through the fovea shows evidence of multiple cystoid elevations in the inner retinal layers suggestive of foveoschisis.

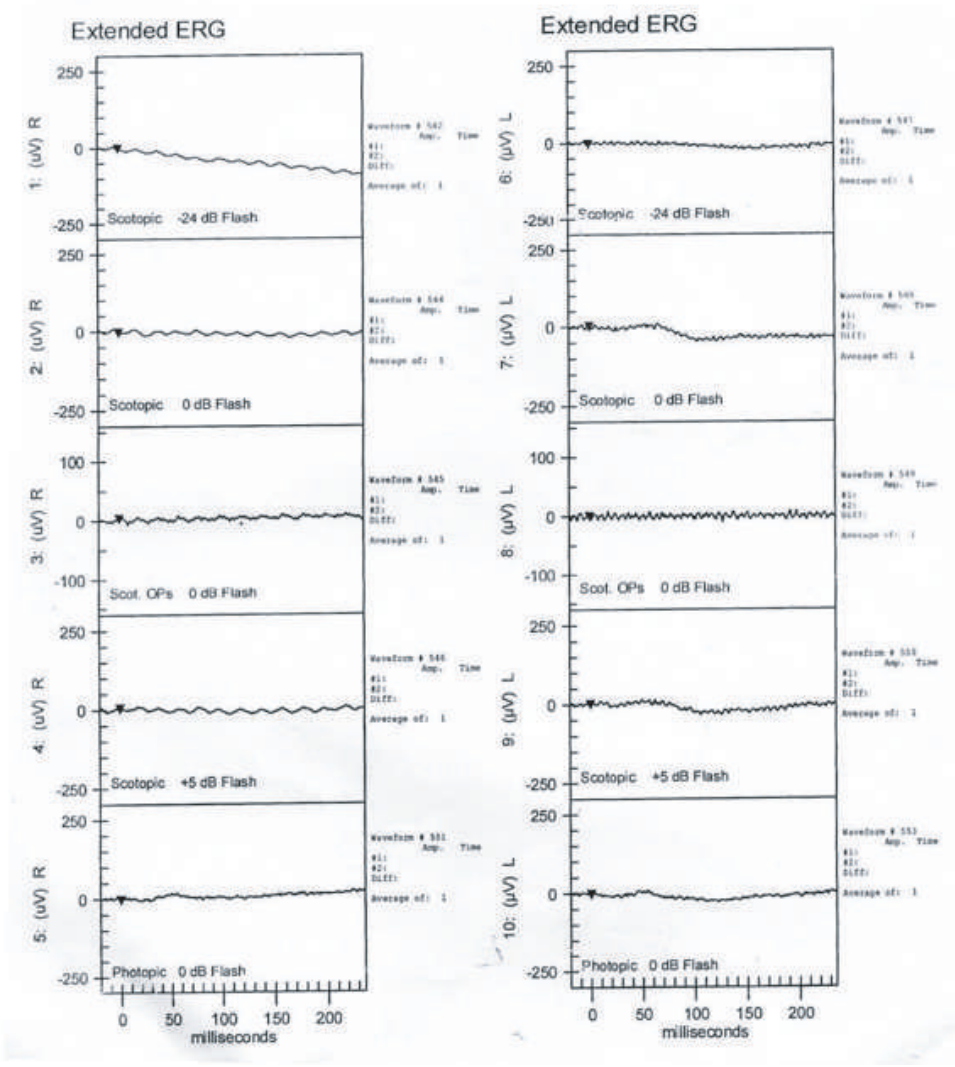

Figure 4. Electroretinogram of the patient shows evidence of extinguished wave response in both eyes.

mode of inheritance. No autofluorescence or clinical evidence of optic nerve head drusen was noted. They postulated that posterior microphthalmos and retinitis pigmentosa may be the constant features of the syndrome, while foveoschisis and optic nerve head drusen may exist as variable features of this syndrome.

In a study of four families, phenotypic variability was reported with PMPRS arising due to *MFRP* gene mutations.[7] The authors noted a variable

presence of optic nerve head drusen, serous retinal detachments, and foveal cysts. Contrary to reports of Nasser et al,[12] no subretinal drusenoid deposits or craniofacial malformations were noted in our case.

Albar and co-authors[13] reported a case of high hyperopia that was managed with bilateral clear lens extraction and posterior chamber intra-ocular lens implantation. Although a diagnosis of PM was reached, the authors attributed the foveoschisis to be a postoperative cystoid macular edema for which repeated intravitreal injections of anti-VEGF and steroids were administered. It is pertinent to note that a high index of suspicion in, and a knowledge of retinal pathologies that coexist with, posterior microphthalmos may prevent such futile treatments in patient with high hyperopia.

In conclusion, cases with high hyperopia should be suspected with PM which can occur with other ocular and systemic features. Its correct interpretation is important to avoid the misdiagnosis and subjecting the patient to unnecessary investigations and interventions. Amblyopia therapy and close follow-up is important to improve or maintain visual function that may be compromised due to the existing retinal pathologies.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for his images and other clinical information to be reported in the journal. The patient understand that her name and initial will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Financial Support and Sponsorship

None.

Conflicts of Interest

None.

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Photo Essay

Congenital Retinal Macrovessel; Optical Coherence Tomography Angiography Features

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J Ophthalmic Vis Res 2023; 18 (2): 245–248

PRESENTATION

Congenital retinal macrovessel (CRM) was first described by Mauthner in 1869 and was further classified by Brown in 1982 as an aberrant retinal vessel that crosses the horizontal raphe in the macular region. Abnormal fetal development between the 15^{th} and 16^{th} weeks of embryogenesis is thought to cause CRM.[1]

A 60-year-old otherwise healthy woman presented to our clinic complaining of gradual decreased vision in the right eye. The best-corrected visual acuity was 20/40 refracting with +1.00 –1.00 × 180. Complete ocular examination revealed no pathologic findings except mild nuclear sclerosis cataract in both eyes. Fundus examination revealed an aberrant vessel crossing the horizontal raphe in the macular region in the right eye.

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Received: 05-05-2020 Accepted: 22-06-2022

Access this article online

Website: https://knepublishing.com/index.php/JOVR

DOI: 10.18502/jovr.v18i2.13191

Figure 1 shows the fundus photograph, infrared image, and fluorescein angiography of the right eye. An aberrant retinal vessel that originated from the inferotemporal part and moved toward the superior part of the macula is evident in all images. Telangiectatic capillaries are also seen at the distal part of the branches.

The optical coherence tomography angiography (OCTA) illustrates an abnormal aberrant vessel in the inferior part of the macula crossing the center. There are also large and small vessels making connection between the aberrant vessel and the superior and inferior macular main vessels in both superficial and deep layers [Figure 2]. The images demonstrating outer segments shows that the aberrant vessel did not penetrate deeper than the outer nuclear layer (ONL). Flow-overlay images show the presence of blood flow in these vessels. Besides, the unusual and distorted shape of the foveal avascular zone (FAZ) is also evident [Figure 2].

How to cite this article: Nourinia R, Hassanpour K. Congenital Retinal Macrovessel; Optical Coherence Tomography Angiography Features . J Ophthalmic Vis Res 2023;18:245–248.

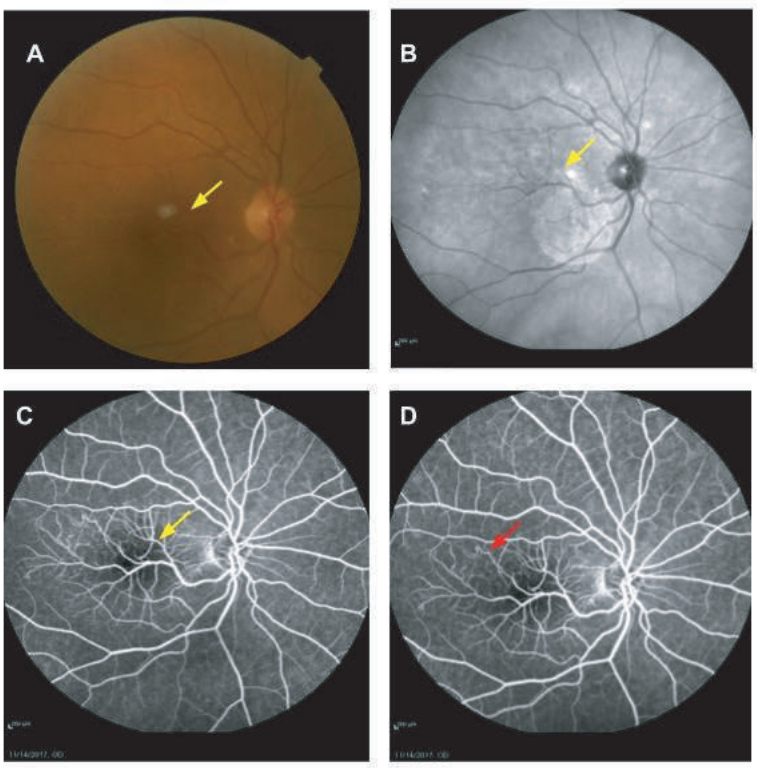

Figure 1. (A) Fundus photograph of the right eye showing a dilated, retinal vein moving toward the macula and crossing the horizontal raphe, suggestive of a venous congenital retinal macrovessel (CRM). (B) Corresponding infrared image shows the aberrant vessel where its first and second branching cross the horizontal raphe in the macular area. Abnormal telangiectatic vessels are seen at the end of the branches. (C & D) Fundus fluorescein angiography confirmed a venous CRM with draining venules crossing the horizontal raphe (yellow arrow), and telangiectatic capillaries are seen at the distal part of the branches (red arrow).

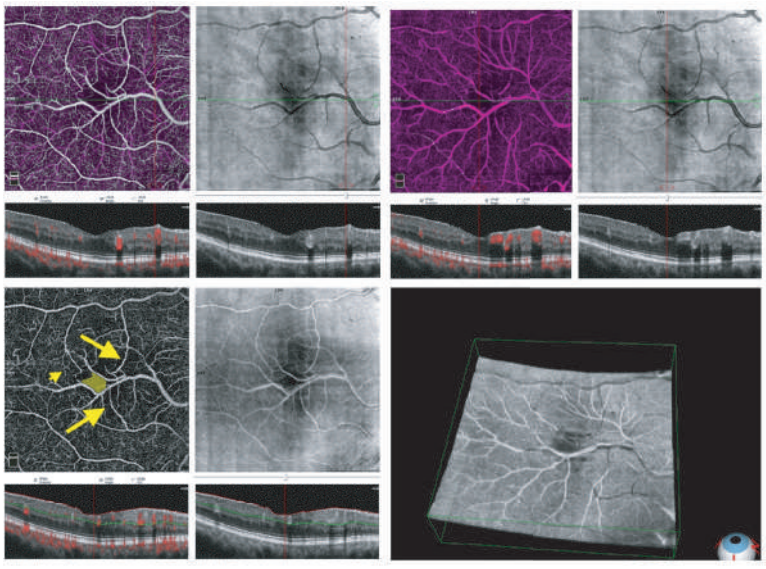

Figure 2. C-scan image of optical coherence tomography angiography shows a large aberrant vessel crossing the center of the macula, and an unusual shape of the foveal avascular zone. Large vessels that connect the superior and inferior main vessels to the aberrant vessel are also evident (large arrows). Similarly, small vessels connect the superior and inferior vessels to the aberrant vessels (in both deep and superficial layers; small arrowhead). The B-scan image of the optical coherence tomography angiography shows the sections of the aberrant vessel adjacent to the foveal center.

DISCUSSION

CRMs are usually unilateral incidental findings without any visual symptoms which are most possibly of venous origin. However, the association between CRMs and many other retinal pathologies including central serous chorioretinopathy (CSCR), retinal hemangioma, microaneurysm, and rhegmatogenous retinal detachment have been reported.[2] Moreover, other vascular abnormalities including brain venous malformations are also reported in association with CRMs. Therefore, neuroimaging is recommended to find any malformation in brain vessels.[3]

Multimodal imaging of a CRM provides a better understanding of the nature of aberrant vessels. OCTA allows for the separation of deep and superficial capillary plexus which results in a better demonstration of the levels and paths of aberrant vessels.[2, 4] In our case, we manually adjusted the segmentation of the OCTA. The dominance of these aberrant vessels in the deep capillary plexus (DCP) might confirm its nature to be venous in origin as DCP is considered the layer more responsible for venous drainage.[5] Another advantage of OCTA is that concurrent vascular pathologies like retinal hemangioma or choroidal neovascularization can be simultaneously ruled out.

Financial Support and Sponsorship

None.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. The patient has given her consent for the use of images and other clinical information to be reported in the journal. The patient understands that her name and initial will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Conflicts of Interest

The authors declare no conflict of interest.

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