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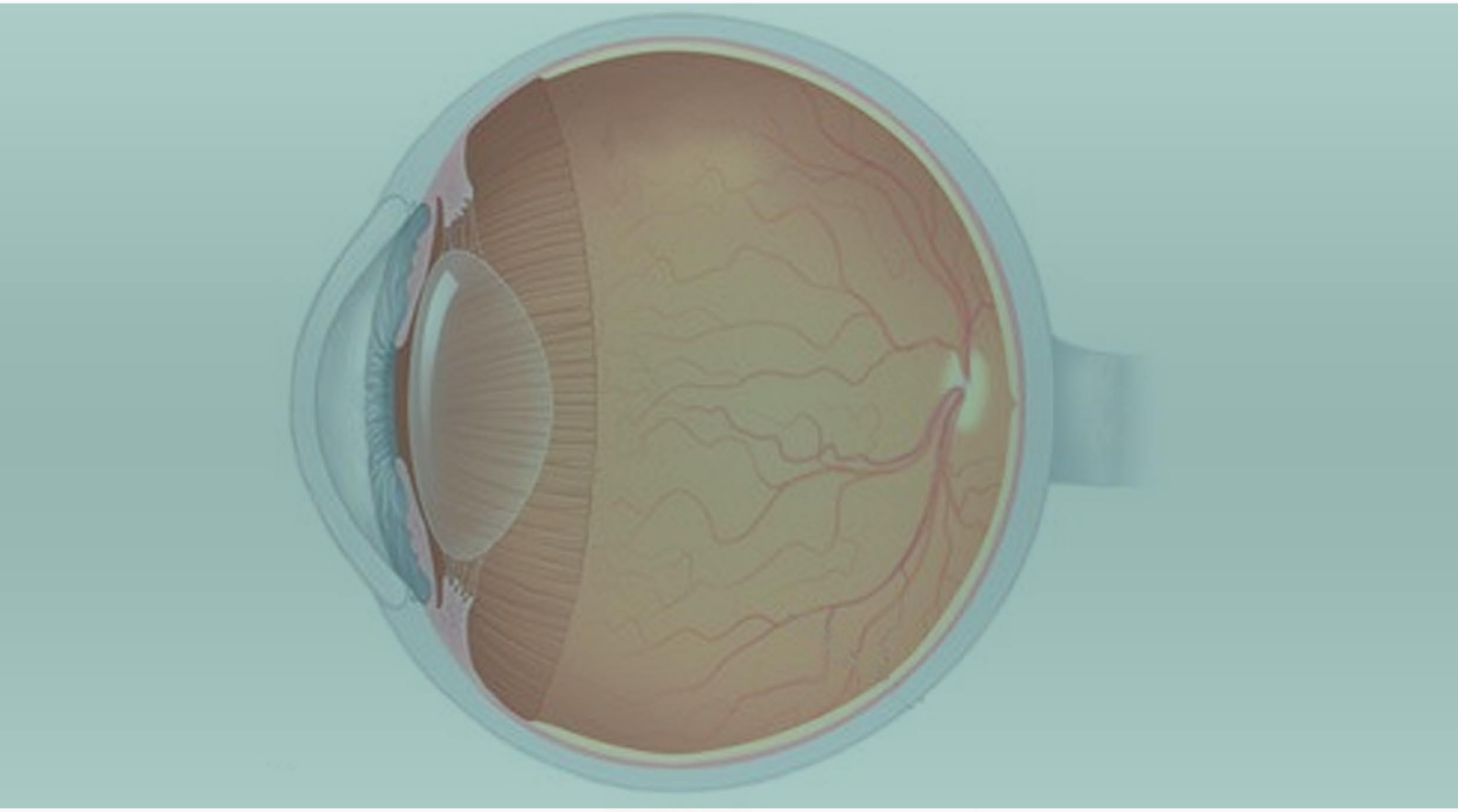

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Editorial

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Dry Eye Post Surgery Update

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A number of studies have mentioned high incidence of asymptomatic dry eye syndrome before cataract surgery and more specifically refractive surgery with Excimer Láser. Ocular surgeries play an important role that can trigger or exacerbates this condition.[1]

According to the new definition in the DWES II Report: *"Dry eye is a multifactorial ocular surface disease, characterized by a tear film loss of homeostasis, accompanied by ocular symptoms, in which tear film instability, hyperosmolarity, ocular surface inflammation and damage and neurosensory abnormalities play etiological roles"*.[2]

The prevalence of dry eye in the USA is around 11-33% and is directly proportional to age.[3] The main objective to reduce or eliminate dry eye symptoms completely is by implementing new strategies of pre-surgical diagnosis and management.

Recent advances in the field of refractive surgery have prioritized visual quality as a primary clinical parameter in the treatment of these patients. Dry eye symptoms are one of the most frequent causes of complaints of those patients who undergo refractive or cataract surgery, most often in the immediate post-operative phase. The patients who undergo cataract surgery show relatively higher chances to present dry eye symptoms following surgery, and most commonly disappears within a short span of time.

For this reason, it is important to consider the detection for dry eye syndrome prior to any ocular surgery. In cases where this is confirmed, an appropriate treatment should be performed prior to the proposed surgical procedure, because otherwise one runs the risk of suffering associated complications, for example, error calculation for intraocular lenses in cataract surgery or low post-operative visual quality in refractive surgeries.[4]

Patients who already experienced dry eyes before surgery underwent greater discomfort and slower recovery. For some of these patients, most frequently the elderly, who already suffered from dry eyes before surgery, the use of peri-surgery medication, intensive treatment with antibiotics, anti-inflammatory drugs and other highly used drops can result in toxic effects to the ocular surface and consequently lead to dry eye.

On the other hand, the inflammatory processes generated during the surgery can lead to tear accessories gland damage, which can be further aggravated in prolonged surgeries (the complicated ones or surgeries performed by residents in training who lack adequate experience) based on the application of photolysis for extensive thermic impact on the ocular surface following an exposure to the light microscope.

During phacoemulsification the neurological damage is relatively lesser due to refractive surgeries.

On the basis of our knowledge, the cornea is densely populated by sensory nerves originating from the trigeminal ganglion ophthalmic division and the autonomic nervous system; parasympathetic fibers and lesser number of sympathetic nerves arising from the superior cervical ganglion. Corneal nerves are divided into branches in the peripheral cornea.

Some of these branches are connected with each other creating the stromal neural net-

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work; however, most of these branches penetrate through the epithelium, to create long beam which supplies the central epithelium. Two of the most commonly performed refractive surgeries, photorefractive keratectomy (PRK), laser assisted *in-situ* keratomileusis (LASIK), lead to damage of the corneal nerves.

In the PRK procedure, the excision of the corneal epithelium damages the epithelial nerves. The application of laser beam in surgery has also been associated with damage to the anterior stromal nerves in the ablation area; therefore, a commonly encountered PRK complication is dry eye. It has been observed that a long-term damage to the ocular surface, (2 years following the PRK surgery) showed a roughly 80% chance of neuronal corneal density recovery. Existing reports suggest that even 5 years after the PRK procedure, some of the patients have still not been able to recover their normal sub-basal neuro-morphology.

Having mentioned this, is clear that, after refractive surgery, the regeneration of the corneal nerves becomes a prerequisite in order to ensure a complete recovery of the ocular surface.

With respect to LASIK, the disruption of the corneal nerves while performing the flap and subsequent photo ablation, is the main cause of post-LASIK dry eye symptoms, thus being associated with the most significant adverse effect of this procedure. It has been reported that in the long-term, post-LASIK damage, up to 95% of the patients may experience dry eye symptoms, 60% of which experience mild to severe dry eye symptoms during the 1st month post-surgery, while some keep on experiencing these symptoms in the long-term, with a chronic incidence of dry eye ranging from 20% to 50%, 6 months after the surgery.[5]

It has been observed that nerves can regenerate after LASIK, but even 5 years after the surgery, the neuronal density seems to be lesser than that prior to surgery. There has been a decline of 90% of the central nervous fibers density during the post LASIK phase in the first month, which could take years to restore to the normal values, pre-surgery.

The reduction in neural innervations has diminished the corneal sensitivity, disrupting the interaction between the afferent sensory nerves of the ocular surface and the efferent autonomous nerves of the tear glands. Other mechanisms suggested, such as blinking frequency reduction may increase the tear evaporation rate. Damage to the corneal epithelium increases the levels of pro-inflammatory cytokines and interleukins (IL-6, IL-8) in tears.

During the application of suction rings and the use of microkeratome, Goblet cells are lost resulting in a decrease in the secondary mucin secretion, which when existing normally would stabilize the tear film and avoid the evaporation.

A decrease in the density of nerve fibers causes affects not only in the tear film quality, but also the tear secretion, decreasing the blinking rate and the wound healing property of the epithelium. All these factors are associated with the pathogenesis of post-refractive surgical dry eye.

A reduction in tear secretion caused due to the suppression of afferent fibers increases the osmolarity. And this generates greater presence of inflammatory substances triggering a cascade with release of chemical mediators (IL-1 alpha and beta, TNF-alpha) and matrix metalloproteinases (MMP-9) thus producing instability of the tear film.[6]

In patients with a history of dry eye, it is important to take it into account, the osmolarity prior to surgery as a reference, since its increase generates more chances to present post-operative discomfort.[7]

Medical attention should be given to reduce the risks and control factors that induce dry eye such as toxic substances, systemic drugs, contact lenses, environmental factors, systemic diseases, nutritional parameters, anxiety and chronic stress. The tear film stability needs to be improved with the use of lacrimal occlusions, artificial tears improving the lipid layer, a lid margin exfoliation and meibomian gland probing. The application of corticosteroid pulses, immunosuppresses such as tacrolymus, cyclosporine A-MMP-9 inhibitors, doxycycline 50 mg/d. can help improve inflammation, infection and osmolarity associated with dry eyes. The treatment strategy should be aimed towards improving the tissue status by providing vitamin A and artificial tears with protector effects and mediating the use of 20% autologous serum and therapeutic contact lenses, which are important tools for the conventional treatment of dry eyes.

The new therapeutic approaches include the recommendation of the intake of essential fatty acids omega 3 (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) intake before ophthalmological surgery, aiming to prevent and treat any post-surgical dry eye conditions. The indicators of the tear film show to have greater stability with the additional effect it provides the diet rich in omega 3 pre- and post-surgery.[8]

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It is very important to ensure that source of the omega 3 is seafood and not vegetables (chia or flax). Several studies have showed that following the intake of ALA chia capsules, only 5% of its composition transforms into EPA and <0.5% into DHA, leaving behind an insignificant fraction of the useful constituent, thus leading to the conclusion that the anti-inflammatory effects of chia capsules is too low.[9]

The Omega 3 supplement with EPA and DHA functions in many ways to relieve and to treat the symptoms of dry eyes, improving the quality of the secretion of meibomian glands, stimulating aqueous tear secretion by the affected lacrimal glands, reparation and reduction of apoptosis in the tear gland, and eliminating inflammation in the conditions of blepharitis and meibomitis.

Omega 3 has also been observed to improve the potential neuronal regeneration (with higher epithelial subbasal neuronal cells plexus proliferation after surgery). The DHA supplementation improves neuronal regeneration after lesion, increasing anti-inflammatory activity and supporting the recovery of goblet cells that increase the levels of secreted mucin, improving the adherence and permanence of the tear to the ocular surface.[10,11]

It most be considered in some way that during the prelude of cataract surgery, the corneal epithelium must be protected, and the use of 2% hydroxypropyl methylcellulose is recommended for proper hydration, thus reducing the symptomatology of dry eye syndrome.[12] Also Nepafenac 0.1% was safe for corneal epithelium after phacoemulsification.[13]

Another new alternative is the use of IPL (Intense Pulsed Light) because it has led to the improvement of dry eye symptoms post-surgery to show an analgesic, anti-inflammatory, anti-microbial (Bacteria's and Demodex) effect and a biostimulatory and neurotropic activity.[14] On the basis of the general principle underlying Arndt Shuktz's Law in the Phototherapy, IPL has been observed to accentuate the vital cells activity.

The analgesic effect of IPL lowers the concentration of the mediators of inflammation (such as cytokines and interleukins) which activate the pain receptors.[15] Decreasing the threshold of the pain when the ionic concentration is stabilized on both sides of the cellular membrane during sensitive terminations affects the sensory nerve fibers thereby delaying neuronal depolarization.

Also, it has an effect on the central nucleus of pain by activating the thalamus and blocks perception of pain by increasing the endorphin and beta-endorphins levels.

The anti-inflammatory effect of IPL in local vasodilatation is attributed to a thermal effect and the partial blockage of a precapillary sphincter with a marked increase in the histamine levels and nitric oxide concentration, a greater oxygen and nutrient supply and reabsorption of edema and necrotic material from the inflamed area.

IPL has a direct antimicrobial effect against bacteria, viruses, fungi and mites.

Biostimulation and tissue regeneration is thus facilitated, which is associated with increased cellular mitosis and tissue repair, increased collagen and fibroblast production and an improvement in the neuro-trophic activity.[16]

Although, Omega 3 and IPL treatment strategies did not demonstrate local or systemic adverse effects; however, further studies are necessary to confirm these potential benefits of the mentioned dry eye post-surgery treatment approaches.

In conclusion, while dry eye is a pathology of the ocular surface (understood as a functional unit), it is important to consider that many patients already suffer this condition prior to performing ocular surgeries. Most of these patients are asymptomatic and needs objective studies that allow a correct diagnosis and treatment avoiding inaccurate pre-operative measures or improving the post-operative refractive results. In general, dry eye is not an absolute contraindication for many eye surgeries, but should be considered and treated appropriately to achieve the desired welfare effect according to the surgical procedure performed.

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Retrospective Study

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Clinical Spectrum of Pediatric Optic Neuritis in Indian Children

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ABSTRACT

Purpose: To study the clinical spectrum of pediatric optic neuritis in Indian children at a tertiary care centre.
Methods: A retrospective study of patients diagnosed with optic neuritis below 20 years of age at a tertiary care centre in India over a 3 year period were reviewed. The ophthalmological examination findings, Goldmann perimetry, electrophysiological tests and magnetic resonance imaging (MRI) were reviewed.
Results: The study reviewed 28 patients (44 eyes) and found a mean age of 12.6±4.9 years (2-20 years) having a follow-up record for a mean period of 6.3±4.9 months (0.3-38 months). 32.1% were females (F: M-0.47). Six patients (20.7%) had a viral prodrome and 12 (42.9%) complained of painful ocular movements. The mean baseline visual acuity (VA) was 1.80±0.6 logMAR units (Range=0.2-3.0 logMAR units) and the last best visual acuity was 0.43±0.4 log MAR units (Range=0-1.79 logMAR units). Thirty six eyes (81.8%) had a visual acuity at or below 3/60 and 40 eyes (90.9%) of 6/60 or lower of the snellen chart at the time of presentation. The mean contrast sensitivity at presentation was 1.02±0.46 (range=0-1.65). 16 pts (57.1%) had a bilateral presentation and 20 patients (71.4%) had either unilateral or bilateral papillitis. All the patients were given pulse dexamethasone (3-5 mg/kg/d) for three consecutive days followed by oral prednisolone (1-1.5 mgKg/day) for 11 days. At 1 week, 21 out of 44 eyes (47.7%) had a visual acuity ≥6/18 of the snellen chart. Three patients showed demyelination suggestive of multiple sclerosis (MS) on MRI brain and were diagnosed as probable MS. A total of 9 eyes (20.5%) of 6 patients (20.7%) had a recurrence. Those below 10 years of age presented more commonly with papillitis compared to teenagers (p value=0.01). All the parameters were similar in males and females.
Conclusion: Pediatric optic neuritis patients are associated with a good visual outcome and a faster recovery. There are no gender differences in either the presentation or the visual recovery. Papillitis was more often seen in the children below 10 years of age. None of the patients developed clinically definite multiple sclerosis.

KEY WORDS: Optic neuritis; Pediatric; Childhood; Clinical profile; Visual outcome.

ABBREVIATIONS: MRI: Magnetic Resonance Imaging; MS: Multiple Sclerosis; NMO: Neuromyelitis optica; ONTT: Optic Neuritis Treatment Trial; VEP: Visual Evoked Potential.

INTRODUCTION

Optic neuritis refers to inflammation of the optic nerve. Inflammation of the optic nerve causes loss of vision usually due to the swelling and destruction of the myelin sheath covering the optic nerve. Direct axonal damage may also play a role in nerve loss in many cases. The most

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common aetiology in adults is multiple sclerosis (MS) while that in children is considered to be parainfectious.

Symptoms of optic neuritis include sudden loss of vision with an afferent pupillary defect in the involved eye, pain on movement of affected eye, and impairment of visual functions such as color vision, contrast sensitivity and visual fields. Typically, there is spontaneous recovery of vision and this has been shown to get accelerated by steroids.

Optic neuritis affects children less commonly than adults. Optic neuritis in children may occur as an isolated episode having, presumably, a self-limited course and carrying no prognostic implication with respect to the rest of the nervous system. Other cases may be followed by development of MS, neuromyelitis optica (NMO) or Schilder's disease. Majority of the information about pediatric optic neuritis comes from western literature and the data is sparse in Asian countries. Furthermore, since optic neuritis treatment trial (ONTT) excluded patients with pediatric optic neuritis, little is known about its spectrum and outcome.[1] It has been observed that the clinical profile and outcome of optic neuritis among adults in the Western population differs significantly from that in the East and this may hold true for pediatric optic neuritis.[2]

The purpose of this study is to retrospectively review the cases of optic neuritis among a population of less than 20 years of age at a tertiary care hospital in order to understand the various clinical aspects of these patients and compare it with the Caucasian population.

MATERILAS AND METHODS

A retrospective study was performed on all patients <20 years of age who presented with optic neuritis at the neuro-ophthalmology clinic of a tertiary care Apex Eye Hospital in New Delhi, India over a 3 year period. The upper age limit used to define the pediatric population varies among experts, including adolescents and up to the age of 21 is consistent with the definition found in several well-known sources.[3-5] The study was approved by the Institutional Review Board. Retrospective review of the medical records of patients with a diagnosis of optic neuritis that came to a tertiary care centre during a 2 year period was done. Searches identified a total of 29 consecutive cases that were eligible for inclusion. One patient developed transverse myelitis early on follow-up and was therefore excluded from the analysis.

The diagnosis of optic neuritis was made clinically on the basis of an acute or sub-acute vision loss in one or both eyes with one or more of the following findings; pain on eye movements, optic nerve swelling, relative afferent pupillary defect in unilateral cases, dyschromatopsia, abnormal visual evoked potentials, and no other identifiable cause. The patients with neurological findings, acute disseminated encephalomyelitis or other central nervous system (CNS) causative etiology, neuroretinitis, compressive or infiltrative optic neuropathies and Leber's hereditary optic neuropathy were excluded. Patients with other concurrent ophthalmic ailments (other than refractive error) were also excluded.

Demographic and clinical information collected for each patient included age at onset, gender, ethnicity, best corrected visual acuity at presentation, prodromal symptoms, preceding illnesses, ocular examination, relevant laboratory findings (where available/done: hemogram with ESR, serum electrolytes, quantiferon gold assay for mycobacterium tuberculosis, blood culture and sensitivity, where appropriate and autoimmune workup including antinuclear antibodies (ANA), antineutrophil cytoplasmic antibody (ANCA) and radio frequency (RF), where appropriate), perimetry, visual evoked potential (VEP), neuro-imaging, treatment, and follow-up data. Abnormal magnetic resonance imaging (MRI) was defined by the presence of one or more T2-hyperintense lesions on brain MRI.

Bilateral optic neuritis was defined as, both eyes involved simultaneously or within 4 weeks of each other, and recurrent optic neuritis was diagnosed when the repeat attack affected one or both eyes after an interval of more than 4 weeks. This is similar to the criterion used for the diagnosis of 2 demyelinating episodes/attacks in MS patients.[6]

Patients were subgrouped on the basis of age and gender, and the subgroups were then compared for various clinical parameters.

An excel spreadsheet was designed to collect the data and statistical analyses were performed using the SPSS (version 14.0; SPSS Inc., Chicago, IL, USA). Qualitative data were expressed as percentages and quantitative data were expressed as mean±standard deviation or median and range. Data with parametric distribution were analyzed using the Mann Whitney U-test and those with non-parametric distribution were analyzed using the Chi Square test. A p-value of <0.05 was taken as statistically significant.

RESULTS

The study included 28 patients (44 eyes) who had presented to the neuro-ophthalmology clinic over a 3 year period with a mean follow-up of 6.3±4.9 months (0.3-38 months). The mean age of the study patients was 12.6±4.9 years (2-20 years). There were 19 males (67.9%) and 9 (32.1%) females. Two children were below 5 years of age.

A review of the past medical history revealed no significant ophthalmic disorders, injuries or illnesses. None of the patients were under any medication, there were no known drug allergies and all of them were fully immunized for their age. There was no family history of ophthalmic disease. The neurological examination was normal except for the optic nerve abnormalities. Laboratory tests showed leukocytosis in 2 patients. All other laboratory tests were negative.

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Table 1: Clinical Features of Patients with Optic Neuritis at Presentation.

Clinical features	Total (% Total)
No. of patients	28 (100%)
Male(M)	19 (67.9%)
Female(F)	9 (32.1%)
F/M ratio	0.47
Age at onset	12.64±4.95 years (2-20 years)
Country of birth-India	28 (100 %)
Family history of MS	00
Eye involvement	
Unilateral	12 (42.8%)
Bilateral	16 (57.1%)
Associated symptoms	
Pain with ocular movements	12 (42.9%)
Other neurologic symptoms	00
Viral prodrome	6 (21.4%)
Recent immunization	00
No. of affected eyes	44 (100%)
Pupils- presence of RAPD	12 (27.2%)
Fundoscopy	
Disc edema Normal (Retrobulbar neuritis)	34 (77.3%) 10 (22.69%)
Visual fields Abnormal 1.Central scotoma 2. Centrocecal scotoma 3. Enlarged blind spot 4. Peripheral constriction of fields Not recordable	 18 (40.91%) 05 (11.36%) 07 (15.92%) 04 (9.09%) 02 (4.54 %) 26 (59.09%)
VEP abnormal	44 (100%)
Follow-up	6.38±4.99 months (Range 0.25-38 months)

The clinical features of the patients are summarized in Table 1. The mean baseline visual acuity of the study patients was 1.80±0.6 logMAR units and the last best visual acuity was 0.43±0.4 log units. 36 eyes (81.8%) had a visual acuity at or below 3/60 and 40 eyes (90.9%) had a visual acuity of 6/60 or lower of the Snellen chart at the time of initial presentation. Four patients had no perception of light at presentation (Figure 1). Overall, the visual acuity loss was severe in majority of our patients (Table 2). Papillitis was present in 20 patients (71.4%) (Figure 2). The remaining patients had normal fundi (retrobulbar neuritis (RBN)). The presentation was bilateral in 16 (57.1%) patients. Of these patients with a bilateral presentation, 87.5% (12 patients) had papillitis.

All the patients were given pulse dexamethasone (3-5 mg/kg/d) for three consecutive days followed by oral prednisolone (1-1.5 mg/kg/day) for 11 days. This was in accordance with the treatment guidelines of the institution where all pediatric optic neuritis patients are given steroids after the baseline investigations rule out an infective etiology. This is to ensure a quicker visual recovery as majority of these cases are bilateral and have profound visual loss. Also, pulse dexamethasone is used in view of better safety and equal efficacy to IV methylprednisolone (as used in optic neuritis treatment trial).[7] The visual acuity improved in all the patients. At 1 week, 21 out of 44 eyes (47.7%) had a visual acuity ≥6/18 of the Snellen chart (Figure 3). Post-treatment assessments were

Figure 1: Visual Acuity at Presentation.

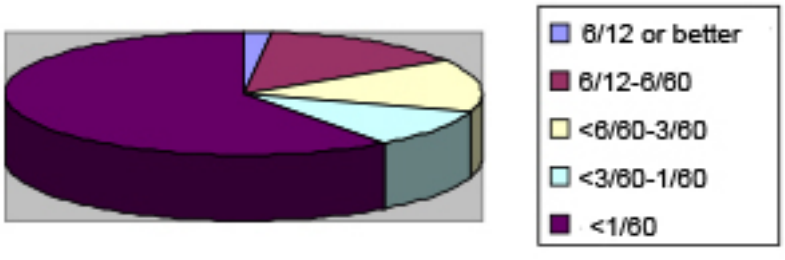

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Table 2: Visual Acuity in 28 Patients of Pediatric Optic Neuritis (44 Eyes).

Visual acuity (LogMAR)	Snellen equivalent visual acuity	Initial VA (Number of eyes (n))	Best attained VA (Number of eyes (n))
0.3 or better	6/12 or better	1	27
<0.3-1	<6/12-6/60	7	13
<1-1.3	<6/60- 3/60	1	0
<1.3-1.77	<3/60-1/60	5	3
<1.77	<1/60	30	1
Total		44	44

Figure 2: Fundus Image of a Case of Papillitis, Taken on a Portable Smartscope Pro (Optomed Oy, Finland) Fundus Camera.

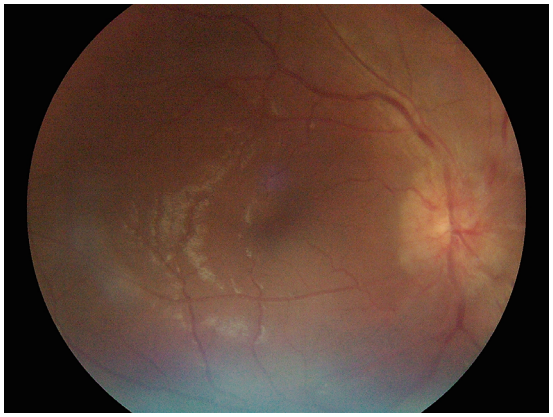
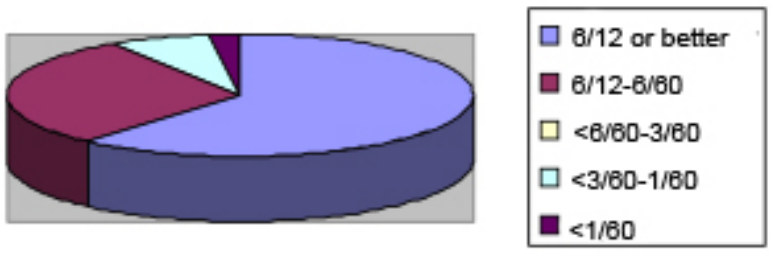


Figure 3: Visual Acuity at Final Follow-up.



individualized for each patient. Generally, the assessments were done at 1 week, 1 month, 1 month, 3 months and 6 monthly thereon. All the patients who recovered to a VA of 6/6 continued to have some amount of disc pallor. The final visual acuity of patients with RBN was 0.504±0.59 (median of 0.2) and in papillitis was 0.408±0.40 (median of 0.3) and the difference was not statistically significant (p=0.83) A total of 9 eyes (20.5%) of 6 patients (20.7%) had a recurrence. Of these, five patients had retrobulbar neuritis and one had papillitis. The median period of recurrence was 2 months (0.5-9 months).

MRI was done in 19 patients (67.8%). MRI showed absence of any demyelinating lesions in the brain (other than the optic nerve) in 14 patients, 3 patients showed lesions suggestive of MS. These patients were 7, 12 and 15 years old and had demyelinating lesions in the brain (other than the optic nerve) at only one of the four typical locations in MS (periventricular, infratentorial, juxtacortical and spinal cord).[5] VEP was done in all the patients and demonstrated increased latency of the p100 wave in all the patients (mean amplitude of 5.5 microvolt and latency 132 msec). Visual fields (Goldmann visual perimetry or GVF) could be charted in 18 eyes and centrocecal/central scotoma was the most common field defect (Table 1).

Nine patients were below 10 years of age. Subgroup analysis of patients aged 0-11 years and 11-20 years is depicted in Table 3. Those below 11 years of age presented more commonly with papillitis (p=0.01) and had bilateral disease, though the difference was not statistically significant (p=0.054). The males and females were very similar in relation to age, laterality, pain

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Table 3: Subgroup Analysis of Pediatric Optic Neuritis Patients According to Age (n=28 Patients).

	Age≤10 years (n=9 patients/17 eyes)	Age=11-20 years (n=19 patients/27 eyes)	*p* value (test used)
Number of males	4/9	5/19	0.599 (Chi square test)
Bilateral	8/9	8/19	0.054 (Chi square test)
Pain on ocular movements	2/9	10/19	0.267 (Chi square test)
Baseline visual acuity	1.84±1.1	1.77±1.3	0.632 (Mann whitney test)
Baseline contrast sensitivity	1.09±0.36	0.97±1.14	0.88 (Mann whitney test)
Number of patients with papillitis	17/17	17/27	**0.013** (Mann whitney test)
Best visual acuity achieved	0.37±0.44	0.46±1.12	0.49 (Mann whitney test)
No. of patients with improvement in visual parameters	10/17	17/27	1.00 (Chi square test)
Recurrence	0/9	6/19	0.159 (Chi square test)

on ocular movements, mean baseline and best achieved visual acuity, mean contrast sensitivity, disc edema and recurrences.

DISCUSSION

In this series, we retrospectively reviewed the medical records of optic neuritis patients, and found 28 patients fitting the eligibility criterion. While this number appears small, pediatric optic neuritis forms nearly 5% of the patients with optic neuritis and this is similar to that reported from the West.[8] Two children were below 5 years of age. Such an early presentation is increasingly been reported. Visudhiphan et al[9] reported cases between 1-2 years of age. The female to male ratio of our study patients was 0.47. This is in contrast to the female preponderance in adult optic neuritis and also the majority of the pediatric optic neuritis studies.[10-19] However, Hwang et al[13] also did not find a female predilection in Korean children.

Vision at presentation was poor in most children with over 90% having a visual acuity of 6/60 or lesser. The vision loss as well as the recovery was similar in male and females (0.62 and 0.57 respectively). Visual recovery was good with 40 eyes (90.9%) gaining a visual acuity of more than 6/60 and 27 eyes (61.4%) gaining more than 6/12 at an average follow-up period of 6.38 months. Children below 10 years of age had a visual recovery similar to those between 11-20 years of age (p=0.49). Kriss et al[14] reported a visual acuity of 6/6 or better in 90% of the patients at 8.8 years of follow-up, Wan et al[19] too reported good visual outcomes with nearly 90% regaining 20/40 or better vision and a study from Thailand has shown 70% cases to have complete visual recovery.[20] Malay children have been shown to have a worse visual outcome in a recent study.[18]

History of a viral prodrome is a common finding in children and differentiates it from adult cases. We could document the history of viral prodrome in 6 (21.4%) patients. Wilejto et al[12] documented viral prodrome in 28% of the optic neuritis patients. Kennedy et al[10] suggested that there is no significantly better visual prognosis in children having retrobulbar neuritis as opposed to those having papillitis. The best corrected visual acuity was similar in patients with papillitis and RBN in our study.

Bilateral involvement, which is common in children with optic neuritis, is present in only about one-third of the adults. In our study, 16 patients (57.1%) had a bilateral presentation. Children below 10 years of age more commonly had a bilateral presentation, though this was not statistically significant (p=0.054). The published data has quoted 42-100% of the pediatric patients to have a bilateral presentation.[10-20]

A second noteworthy ocular finding in pediatric optic neuritis is the large number of patients who had papillitis. Kennedy et al[10] noted that more than 70% of the children had some degree of papillitis, normal discs being noted in only three cases (10%). Other studies have also reported papillitis in as many as 87% of pediatric cases.[21,22] In our study, 77.3% of the eyes had papillitis as the presenting feature. All the eyes (100%) presenting below 10 years of age had papillitis.

Children with optic neuritis carry a relatively low risk of subsequent neurologic disease (13% risk of MS by 10 years of age, 19% by 20 years of age, 22% by 30 years of age, and 26% by 40 years of age).[13,18-23] Recurrences were noted in 6 eyes of 9 patients in this study. Of these, MRI of 3 patients showed lesions suggestive of MS but did not confirm to the diagnosis of clinically definite MS and was diagnosed as 'Probable MS'. It is difficult to predict the risk of MS because of a shorter follow-up and needs a long-term study.

A comparison of the clinical profile and risk of multiple sclerosis of Indian patients and Caucasian population has been shown in Table 4.

To conclude, pediatric optic neuritis patients are present with poor vision but are associated with a good visual outcome and a faster recovery. There are no gender differences in either the presentation or the visual recovery. Papillitis was more often seen in the children below 10 years of age. None of the patients developed clinically definite MS.

DISCLAIMER

There is no conflict of interest, financial or otherwise with regard to this study.

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Table 4: Table Depicting Comparison of Caucasian Population and Indian Population with Regard to Clinical Profile of Pediatric Optic Neuritis.

Parameter	Wan et al[25]	Jayakody et al[26]	Wilejto et al[27]	Bonhomme et al[28]	Alper et al[29]	Current Study
Country	USA	USA	Canada	USA	USA	India
Number of cases	46	26	36	29	30	28
Age	12.6 (3.9-18.8)	11.2 (4.5-19)	12.2 (2.2-17.8)	9.6(4.3-16)	10.2 (3.4-16.9)	12.6 (2-20)
M:F ratio	13:33	6:19	5:30	8:21	14:16	19:9
Unilateral:Bilateral	27:19	14:12	21:15	13:16	20:30	12:16
Papillitis	31	19	NA	NA	12	34
Multiple Sclerosis	18	2	14	3	6	3

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Brief Research Report

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The Effect of Intranasal Pressure on Intraocular Pressure

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ABSTRACT

Purpose: The aim of this study was to evaluate intraocular pressure (IOP) after the application of the nasal packing for sinonasal surgery.
Methods: A total of 40 patients who underwent sinonasal surgery were enrolled in this prospective study. Patients were randomly assigned into two groups: gauze packing (group 1) and silicone nasal septal splint (group 2). All participants completed a comprehensive questionnaire and underwent an ocular examination including measurement of IOP by Goldmann applanation tonometry (GAT). All the measurements were repeated before removing the nasal packings. IOP measurements before the operation and during the nasal packing were compared with each other.
Results: The study group comprised 21 males (52.5 %) and 19 females (47.5%). The mean age was 29.10±8.18 years (median 27.50) (min-max=18-51). Twenty-three (57.5%) had silicone nasal packing while 17 (42.5%) had gauze nasal packing. Mean nasal packing duration was 2.575±0.712 days. The post-operative increase in the intraocular pressure of the both eyes were not statistically significant (p>0.05). IOPs of the patients' eyes showed no significant increase, compared to the pre-operative results according to the type of nasal packing used (p>0.05).
Conclusions: Increased intranasal pressure due to nasal packing did not increase intraocular pressure. The type of the nasal packing also did not differ to increase the intraocular pressure.

KEY WORDS: Intranasal pressure; Intraocular pressure; Nasal packing; Glaucoma.

ABBREVIATIONS: IOP: Intraocular pressure; GAT: Goldmann Applanation Tonometry; INP: Intranasal pressure; CI: Confidence Intervals; ABP: Arterial Blood Pressure.

INTRODUCTION

Nasal surgery is one of the most frequently performed operations in otolaryngology practice. Various nasal packs have been used after septal surgery to stabilize the mucoperichondrium and bleeding.[1] Nasal packs increase intranasal pressure (INP).[2] The orbit, nose, and paranasal sinuses are intimately related.[3] Human nose is well vascularized with arteries and veins, and thus supplied with abundant blood. Nasal veins have no vessel valves and direct communication to the sinus caverns. Venous drainage of the nose and sinuses is *via* the ophthalmic and facial veins, and the pterigoid and pharyngeal plexuses.

Intraocular pressure (IOP) is a function of aqueous humor production and subsequent drainage *via* the trabecular meshwork to ophthalmic veins and cavernous sinus. IOP is thus influenced by anything that increases production or decreases drainage of the aqueous humor

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including age, physical exertion, and medications and other factors.[4] Therefore, IOP may be influenced by increased INP.

Glaucoma is a common, multifactorial disease. IOP, one of the most important risk factors for the development and progression of glaucoma is associated with various systemic and ocular factors.[5,6] Clinical studies have demonstrated that certain patients with primary open-angle glaucoma suffer from reduced ocular blood flow, which may be primarily of vascular origin or secondary to IOP elevation.[7]

The aim of this study was to evaluate IOP after the application of the nasal packs for sinonasal surgery. Herein we present such a study to answer these features.

MATERIALS AND METHODS

This study was conducted in the Otolaryngology and Head & Neck Surgery and Ophthalmology Departments between March 2014 and June 2014. Patients (n=40) who had nasal packing after septoplasty due to septal deviation were included in this study. The study procedures were carried out in Haydarpaşa Numune Education and Research Hospital according to the Declaration of Helsinki. The study objectives and methods were explained to all patients before the examination. All the patients signed an informed consent form.

The inclusion criteria were as follows: 1) adult patients aged more than 18 years with a decision to undergo surgery; 2) willingness to sign the informed consent before the study; and 3) best-corrected visual acuity of Snellen equivalent of 20/40 or better.

The exclusion criteria were as follows: 1) previous eye diseases other than refractive error; 2) previous orbital or ocular trauma; 3) previous nasal surgery 4) previous systemic disease; 5) history of allergic rhinitis.

The patient subsequently underwent sinonasal surgery under general anesthesia. All of the patients received nasal packing after surgery. Patients were randomly assigned into two groups: gauze packing (group 1) and silicone nasal septal splint (group 2). Bilateral anterior gauze nasal packing impregnated with Vaseline were applied in one group while silicone nasal septal splints with integral airway were applied in the other group. Gauze nasal packing were cut into three strips and were placed enough to fill the nose. Silicon nasal splints were sutured to the septum and no another type of nasal packing was used.

All of the participants completed a comprehensive questionnaire and underwent an ocular examination including measurement of IOP by Goldmann applanation tonometry (GAT; Haag-Streit; Haag-Streit AG, Koeniz, Switzerland), once for each eye from right to left, prior to the perimetry and fundus photography before the surgery. The IOP was measured in mmHg unit. Ophthalmic signs were bilateral in nature and there were no ophthalmic manifestations including orbital displacement, proptosis, restricted ocular movement, diplopia, lid swelling, chemosis, optic neuropathy, and decreased vision after the surgery. Indirect ophthalmoscopy showed that the retinal arterial circulation was patent to flow.

Nasal packing remained 2 days post-operatively. All the measurements were repeated before removing the nasal packings on the first post-operative day. IOP measurements before the operation and during the nasal packing were compared with each other.

STATISTICS

Statistical analyses of the data were conducted using SPSS ver. 17.0. All variables were calculated using descriptive statistics. The analysis of the quantitative variables included calculation of the mean (SD). Parametric paired sample *t*-test and nonparametric Wilcoxon signed-rank test was used for comparison of two dependent groups. Nonparametric Mann-Whitney U-test was used for the comparison of independent groups. Results were evaluated using the 95% confidence intervals (CI), and the level of significance was set at $p<0.05$.

RESULTS

The study group (n=40) comprised 21 males (52.5 %) and 19 females (47.5%). The mean age was 29.10±8.18 years (median 27.50) (min-max=18-51). Twenty-three (57.5%) had silicone nasal packing while 17 (42.5%) had gauze nasal packing. Pre-operative and post-operative visual examinations were unremarkable. Mean nasal packing duration was 2.575±0.712 days.

The intraocular pressures of patient's eyes were evaluated during nasal packing. Post-operative intraocular pressure of the right eye increased from 15.68 mmHg to 16.55 mmHg (Table 1). However, this increase was not statistically significant ($p=0.115$). Likewise, post-operative intraocular pressure of the left eye increased from 16.00 mmHg to 16.75 mmHg. Again, this was not statistically significant ($p=0.134$) (Table 1).

IOPs of the patients' eyes were evaluated separately according to the type of nasal packing used. There were no significant differences in the pre-operative IOPs between the groups and IOPs in the right eye was within normal limits ($^{a}p=0.750$). There was also no significant difference in the post-operative measurements between groups ($^{a}p=0.200$) (Table 2). For the right eye, the gauze packing and silicone group showed no significant increase, compared to the pre-operative results within the groups ($^{b}p=0.775$, $^{b}p=0.155$) (Table 2).

For the left eye, there were no significant differences in the pre-operative IOPs between the groups and IOPs in the left eye were within normal limits ($^{a}p=0.347$) (Table 3). There was

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Table 1: Pre-operative and Post-operative Evaluation of Intraocular Pressure.

	Pre-op (n=40)	Post-op (n=40)	*p*
	Mean±SD	Mean±SD	
Right IOP (mmHg)	15.68±3.10	16.55±2.81	0.115
Left IOP (mmHg)	16.00±2.76	16.75±3.47	0.134

Paired Samples t-test
**p<0.05*
IOP= Intraocular pressure

Table 2: Comparison of Intraocular Pressure Measurements According to the Nasal Packing in the Right Eye.

	Pre-op IOP (mmHg)	Post-op IOP (mmHg)	First-Last Change
	Mean±SD	Mean±SD	[b]*p*
Gauze (n=17)	15.65± 2.50	15.82±2.21	0.775
Silicone (n=23)	15.70± 3.54	17.08±3.12	0.155
[a]*p*	0.750	0.200	

[a]Mann-Whitney test
[b]Wilcoxon
Signed Ranks test
**p*<0.05
IOP= intraocular pressure

Table 3: Comparison of Intraocular Pressure Measurements According to the Nasal Packing in the Left Eye.

	Pre-op IOP (mmHg)	Post-op IOP (mmHg)	First-Last Change
	Mean±SD	Mean±SD	[b]*p*
Gauze (n=17)	15.59± 2.58	16.24±3.34	0.404
Silicone (n=23)	16.30± 2.88	17.13±3.58	0.296
[a]*p*	0.347	0.441	

[a]Mann
-Whitney test [b]Wilcoxon
Signed Ranks test
**p*<0.05
IOP= intraocular pressure

also no significant difference in the post-operative measurements between groups ([a]p=0.441). The gauze packing and silicone group showed no significant increase, compared to the pre-operative results within the groups respectively ([b]p=0.404, 0.296) (Table 3).

DISCUSSION

The nasal venous circulation can drain directly into both the cavernous sinus and the external nasal venous system. INP causes increased intranasal perfusion pressure, leading to venous congestion and edema. Nasal venous congestion may also affect intraocular venous drainage due to increased pressure in the ophthalmic vein. We evaluated IOP during nasal packing. When the scleral venous drainage is blocked, aqueous humor is secreted at a faster rate than it is reabsorbed, causing elevated pressure within the eye.[8]

Reitsamer et al[9] established that IOP exhibits a linear relationship with ocular venous pressure using a rabbit model. Any significant rise in IOP, decrease in mean arterial pressure, or combination of the two can result in ischemic optic neuropathy or central retinal artery occlusion. Thus, we considered that nasal packing might play a role in increasing IOP.

IOP measurements according to body positions and blood pressures have already been studied previously. It has been shown in several studies that systemic blood pressure changes affect IOP.[10-12] However, a limited number evaluated the venous circulation of the eye.

When a patient is in a prone position, it can elicit an increase in IOP. In a previous study, the effect of the reverse trendelenburg position on IOP was studied in spine surgery patients; the position led to less venous congestion and no patient experienced increased IOP.[13,14] This result indicates that prone position leads to increase in venous pressure. However, there are no data addressing the question of how the orbital venous pressure affects IOP in humans. Higher values are often found in patients in the supine position, probably as a result of an increase in the episcleral venous pressure. Thus, we assessed the effects of increased INP in the human eye.

Li et al[15] evaluated the effects of acute arterial blood pressure (ABP) and venous pressure changes on IOP in rats with experimental glaucoma and revealed that increased venous pressure resulted in a sustained rise in IOP. For this reason, we assessed the effects of increased INP on the human eye. The results revealed that there was an increase in IOP during the nasal packing but this increase was insignificant (p>0.05). However, this increase in IOP was modest. Although we found an insignificant increase, more methodic frequent measurements

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of IOP may detect biologically significant elevations of IOP.

Ekinci et al[16] reported the formation of secondary glaucoma caused by a carotid cavernous fistula. This report showed that increased pressure in the cavernous system may affect the formation of glaucoma. The nasal venous system drains directly into the cavernous sinus. However, nasal packing does not increase cavernous sinus pressure but intranasal pressure can increase the venous congestion.

Previously, Lin et al[17] investigated whether functional endoscopic sinus surgery induced changes in IOP. They revealed that there were no IOP changes. In our study, we also evaluated the effects of different types of nasal packing on IOP. The Vaseline gauze packing applies more pressure on the nasal mucosa, causing more venous congestion. A silicone nasal splint is commonly used in nasal operations and it has a tube in the middle for breathing. This packing applies less pressure to the lateral nasal wall and leads to good quality of life (QoL) post-operatively.[18] We evaluated the intraocular pressure difference in both nasal packing modalities and there was also no significant difference in the post-operative measurements between groups (p>0.05) (Tables 2 and 3). We found that both of these nasal packings could be used safely.

The entire study group was not glaucomatous and the effect was studied in the normal population. Slight increase in the IOP was found to be insignificant in this study although it may be more prominent in glaucomatous eyes. For this reason, it would be better to be more careful in glaucomatous eyes.

CONCLUSION

Nasal packing which are commonly used, increase intranasal pressure. The present study revealed that increased intranasal pressure did not increase intraocular pressure. Also, the type of the nasal packing did not make any difference. Hence, much care should be taken while dealing with glaucomatous eyes.

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No conflict of interest and financial support. The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/eboqLg.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Short Communication

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Evidence-Based Practice in Irregular Cornea Patients' Management With Contact Lenses

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ABSTRACT

Contact lenses (CLs) are safe and commonly used method to correct the refractive errors. Rigid gas permeable (RGP) CLs are the first option in visual rehabilitation of patients with irregular cornea, helping to further delay surgical treatment and improve patients' quality of life (QoL). Although, the practice of CLs in patients with irregular cornea must be based on evidence, there is a lack of Clinical Practice Guidelines (CPGs) developed and assessed under high standards as recommended by the Appraisal of Guidelines for Research and Evaluation (AGREE) (http://www.agreetrust.org/). Current fitting guidelines provided by researchers, practitioners, entities or manufacturers, are generally supported with relatively small clinical studies or cohort studies with owner-designs, providing no-objective pathways to conduct the CL fitting that generally require steep learning curve and practitioners with long experience in CL practice. These recommendations are usually not clinically validated to prove the quality and applicability in new clinical scenarios. CL practitioners require evidence-based guidelines and CPGs that include an objective pathway to choose the CL characteristics like design, geometry, material, etc., with clinically validated support of the recommendations to calculate lens parameters such as back optic zone radius, lens diameter and lens geometry. This practice should be based on clinical research with prospective, randomized and well-designed studies (case-control, cohort, or clinical trials studies) that have been developed and assessed under high standards (AGREE). These new evidence-based guidelines or CPGs will not only improve the safety and transparency of CL fitting procedures, but also guarantee the best patient care with less cost to patients with irregular cornea requiring RGP, improving their vision and QoL.

KEY WORDS: Contact Lenses (CL); Rigid Gas Permeable Lenses (RGP); Irregular Cornea; Clinical Practice Guidelines (CPGs); Disposable Lenses; Frequent-Replacement Lenses; Polymethyl Methacrylate (PMMA) Lenses; Silicone Hydrogel CLs.

SHORT COMMUNICATION

Contact lenses (CLs) are a safe and commonly used method to correct the refractive errors (myopia, hyperopic, astigmatism and presbyopia) with an estimated 140 million users worldwide.[1]

The simplest classification of CLs proposes two major categories based on its composition and make.[2] The first being water based, are generally known as hydrogel or soft CLs (with four different groups, based on the water content and surface electric charge[3,4]) and silicone hydrogel CLs (with different classes of silicon lenses).[4] The second, CLs without water are commonly named as rigid gas permeable (RGP) CLs (polymethyl methacrylate (PMMA) lenses, hard CLs, and gas-permeable CL). While the water based CLs are the most frequently prescribed ones, the ones without water are the least prescribed.[5,6]

RGP CLs allow visual acuity rehabilitation in patients with irregular astigmatism, for example in keratoconus patients,[7,8] after complicated corneal refractive surgery,[9] corneal trau-

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matism,[10] corneal infection[11] or any other eye surgery as corneal transplantation.[12] Moreover, a special design of RGP CLs with reverse geometry (orthokeratology) are prescribed for a long time for temporary myopia correction[13] and have showed a significant amount of reduction in myopia progression.[14,15]

Now-a-days, a huge variety of CLs with varying materials and designs are available to choose from according to one's preference and requirements. Generally, CLs are prescribed with different replacement wearing plans.[6,16] According to the replacement frequency there are two major options: disposable lenses (intended for single use) and frequent-replacement lenses, where the lenses are cleaned and reused depending upon the expiry dates. Likewise, various types of CLs ranging from daily disposable (for one single use), weekly, fortnightly, monthly, three-six monthly to yearly disposable ones are available to suit the user's requirements and specifications (lens material and other factors).[2] Some reports suggest that RGP CLs are generally fitted without a planned replacement schedule[5] and soft CLs are commonly prescribed with fortnightly or monthly replacement schedule.[17]

CLs can be classified in four main categories: daily wear (worn during the day and removed before sleep), extended wear (worn during the day and while sleeping, for periods no longer than six consecutive nights before their removal), continuous wear (worn for up to 30 consecutive nights without removal), and flexible wear (worn daily with an occasional overnight use or during sleep, for example 2-3 nights per week or during an occasional nap).[2] Daily wear is the most commonly chosen option,[17] except in orthokeratology where overnight wear is the primarily prescribed option.[13]

CL practice in patients with irregular cornea must be evidence-based, which means that the conscientious, explicit and judicious use of the current best evidence in making decisions about the care of individual patients must be practised.[18] Preferred practice patterns[19] provide guidance for the pattern of practice and not for the care of a particular individual. Different levels of evidence (Table 1) based on the Scottish Intercollegiate Guideline Network (SIGN)][20] have been proposed and allow to propose different grades of recommendations (Table 2) defined by the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[21-26] Internationally recognized standards have been developed to assess the quality of Clinical Practice Guideline (CPGs) and to guarantee the rigorous development of CPGs. For example, the AGREE II (The Appraisal of Guidelines for Research and Evaluation) (http://www.agreetrust.org/) instrument is a tool, specifically developed for quality assessment of guidelines.[27] Unfortunately, there is not one CL guideline that is assessed under the AGREE requirements now-a-days.

Currently, consensus of experts is the lowest level of evidence but this is commonly used in CLs fitting guidelines, so an increase in research with well-designed studies is necessary to provide sound and evidence-based recommendations to drive CL-practitioners in CL fitting procedure in patients with

Table 1: Levels of Evidence Based on the Scottish Intercollegiate Guideline Network (SIGN).[20]

Level	Type of Evidence
I^{++}	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I^{+}	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II^{++}	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II^{+}	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II^{-}	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Non-analytic studies (e.g., case reports, case series)
IV	Evidence obtained from expert committee reports or experts´ opinion and/or clinical experiences of respected authorities

Table 2: Grades of recommendations defined by the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[26]

Grade	Recommendation
Good Quality (GQ)	Further research is very unlikely to change our confidence in the estimate of the effect
Moderate Quality (MQ)	Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate
Insufficient Quality (IQ)	Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate Any estimate of the effect is very uncertain

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irregular cornea such us keratoconus and other diseases.

The American Optometric Association (AOA) provides a guideline for the care of CL users, based on consensus among experts.[28] Although, this document provides a great reference to CL practitioners, it does not provide specific recommendations to define CL parameters or the range of fitting visits. It mainly focuses on a general description of CL and the most common complications in refractive correction with CL wear, giving limited information about irregular cornea patient management, describing the therapeutic potential of RGP to improve visual acuity and recommending more frequent follow-up visits to these patients. Limited evidence (Level II) supports the different visits (initial or diagnostic visit, dispensing visit and prescribing visit)[29] that confirm the standard CL fitting procedure.

For example, manufactures provide general instructions and recommendations for using their CLs, as well as describing the procedure to calculate the back-optic zone radius (BOZR), lens diameter, lens power, modality of use and replacement, etc. However, most of these recommendations show a lack of evidence behind, especially in describing the CL parameters. Most of these recommendations are based on internal research results, given to the fact that manufacturers are not likely to publish any research/study or instructions in journals which can be accessible to eye care practitioners. These recommendations or guidelines are of paramount importance in RGP CL practice, especially in irregular cornea patients' management with corneal[30] or scleral[31,32] CLs that usually require an experienced CL practitioner.

The BOZR defines soft CL fitting as a simple but much effective procedure that does not require further research. Moreover, manufacturers provide CLs with a limited range of parameters (sometimes with one or two possibilities for example in BOZR or lens diameter). However, it is clearly known that the lens design, material properties, modality of use and replacement, and interaction with lens care system show a significant influence in comfort and user satisfaction.[4] Also, some meta-analyses describe that the risk of an inflammatory complication is mainly related to the material and mode of use.[33] However, with respect to the RGP CLs fitting, the BOZR calculation requires more precision, especially in keratoconus patients with irregular cornea[34] using different methods of fitting the RGP lens (Table 3). In these cases, manufacturers provide different recommendations to calculate the BOZR (with simple equations or with the support of different CL fitting softwares).[35-41] Different equations to define the BOZR of the first diagnostic lens have been provided by manufacturers or research groups. For example, BOZR could be calculated with Kmean (mm),[42] the horizontal K (mm) – 0.10 mm (recommended by Hecht Contactlinsen), or Kmean (mm) – 0.20 mm (recommended by Menicon, Co., Ltd.),[43] or flat K (mm) – [$\frac{1}{3}$astigmatism (mm)] (proposed by Bausch & Lomb), with different equations depending on the corneal astigmatism,[44] or with the flat K-value directly.[45] Nevertheless, it is uncommon that these guidelines include an analysis of the accuracy or precision of the suggested BOZR compared with the finally fitted BOZR that includes results supported with well-designed studies, for example. So, CL practitioners must refine the calculated BOZR assessing the fluorescein pattern to find the correct lens parameters in each case. Most of the CL practitioners believe that RGP CLs fitting process in keratoconus patients is a challenge that requires an increased number of diagnostic lenses and practitioner time or patient chair time to achieve a final acceptable fit compared with standard RGP or soft CL fitting.[39,46-48] A new way to calculate the first diagnosis RGP parameters closer to finally fitted lens design have been proposed[30] showing a BOZR difference less than 0.10 mm in 75% of cases in a prospective cohort study involving a new sample of keratoconus patients. This new nomogram has the potential to reduce the practitioner and patient chair time in order to achieve a final acceptable RGP lens fit in keratoconus patients.

Recently, scleral RGP CLs have been proposed to be fitted in moderate and advanced keratoconus and irregular cornea patients.[49] However, there is a lack of consensus about the fitting procedures (trial sets characteristics, use of validated nomograms),[31] scleral lens design (fenestrated or non-fenestrated, scleral asymmetry approach),[50] wearing time to avoid or reduce corneal oedema,[51] change in lens vault,[52] lens seal-off management, technology necessary to complete the fitting procedure (corneal topography, tomography, and/or optical coherence tomography),[53] etc. that suggest the need for continued research to clarify scleral RGP indications, fitting procedure, regimen of wear and replacement, and complications management.[31,54] Some reports[55] suggest that scleral RGP lenses should be the lens of choice in patients with irregular cornea for visual rehabilitation and delay or prevent further surgical involvement. Yet, this recommendation is proposed with case report studies in-

Table 3: Different Methods of Fitting Corneal GP Lens in Keratoconus Patients (Fitting Philosophies).

Apical clearance	Apical touch	Three-point-touch
Lens support on the paracentral cornea with clearance of the apex	Lens support and bearing on the corneal apex	Lens support between corneal apex and paracentral cornea, showing a peripheral alignment with slight touch at the apex
Acceptable option with small nipple cones but difficult with advanced keratoconus	Better visual acuity but more risk of corneal abrasions and apical scarring	Most widely-accepted and safest modality of GP CL fitting

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volving a few number of patients[32,54] successfully managed with scleral RGP lenses without a comparison with a control group (for example, fitted with corneal RGP CL) in a well-conducted case-control or cohort study. In fact, scleral RGP CLs should be prescribed when other lenses do not provide adequate visual rehabilitation or are not well suitable.[32] Sound fitting guidelines, with objective pathway to choose lens are necessary because scleral RGP CLs fitting requires a steep learning curve, where the practitioner's experience plays a great role in fitting success and more reliable instrumentation to assess scleral and corneal surface is necessary.[31,32]

CONCLUSION

In conclusion, CLs must always be fitted and prescribed by a qualified and competent practitioner after a careful fitting procedure that includes an eye examination to determine whether the CL is suitable for the patient. This will help in minimizing future risk of CL complications.[28] It should be the practitioner's responsibility to prescribe a CL made from a physiologically appropriate material that will induce minimal mechanical impact on the corneal surface while providing the required optical correction to improve the patient´s quality of vision and life.[28,56] However, CL practitioners need to be completely aware of evidence-based guidelines and CPGs that include an objective pathway to choose CL characteristics (design, geometry, material, etc.), with clinically validated support of the recommendations to calculate lens parameters (BOZR, lens diameter and lens geometry), based on clinical research with prospective, randomized and well-designed studies (case-control, cohort, or clinical trials studies), that should be developed and assessed under high standards (AGREE). These new evidence-based guidelines or CPGs will not only improve the safety and transparency of CL fitting procedures, but also guarantee the best patient care with less cost to patients with irregular cornea requiring RGP, improving their vision and quality of life (QoL) significantly.

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Mini Review

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Insights into the Immune System and Glaucoma

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THE IMMUNE SYSTEM HAS BEEN IMPLICATED IN THE PATHOGENESIS OF GLAUCOMA

Glaucoma is a neurodegenerative disease of the optic nerve characterized by progressive loss of retinal ganglion cells (RGCs), which can lead to irreversible blindness. Numerous factors have been implicated in the disease, with high intraocular pressure (IOP), coupled with advanced age, being major risk factors. Other factors include ischemia, generation of reactive oxygen species, a genetic pre-disposition and neurotrophin deprivation in the retina or optic nerve (Figure 1).[1] The pathogenesis of glaucoma is challenging to understand since it is a multifactorial neurodegenerative disease.[2,3] It is even more confounding what causes normal tension glaucoma (NTG). Despite a normal IOP, patients still suffer optic nerve degeneration. The immune system is a probable player in both high tension glaucoma (HTG) and normal tension glaucoma (NTG). Findings from numerous studies support the notion that both the innate and adaptive immune responses are involved in the pathogenesis of glaucoma.[1,3-18] Yet, the precise mechanisms of immune responses and the specific cell interactions contributing to the disease process are still not fully understood. Many questions remain about the role of the immune system in glaucoma (Figure 1).

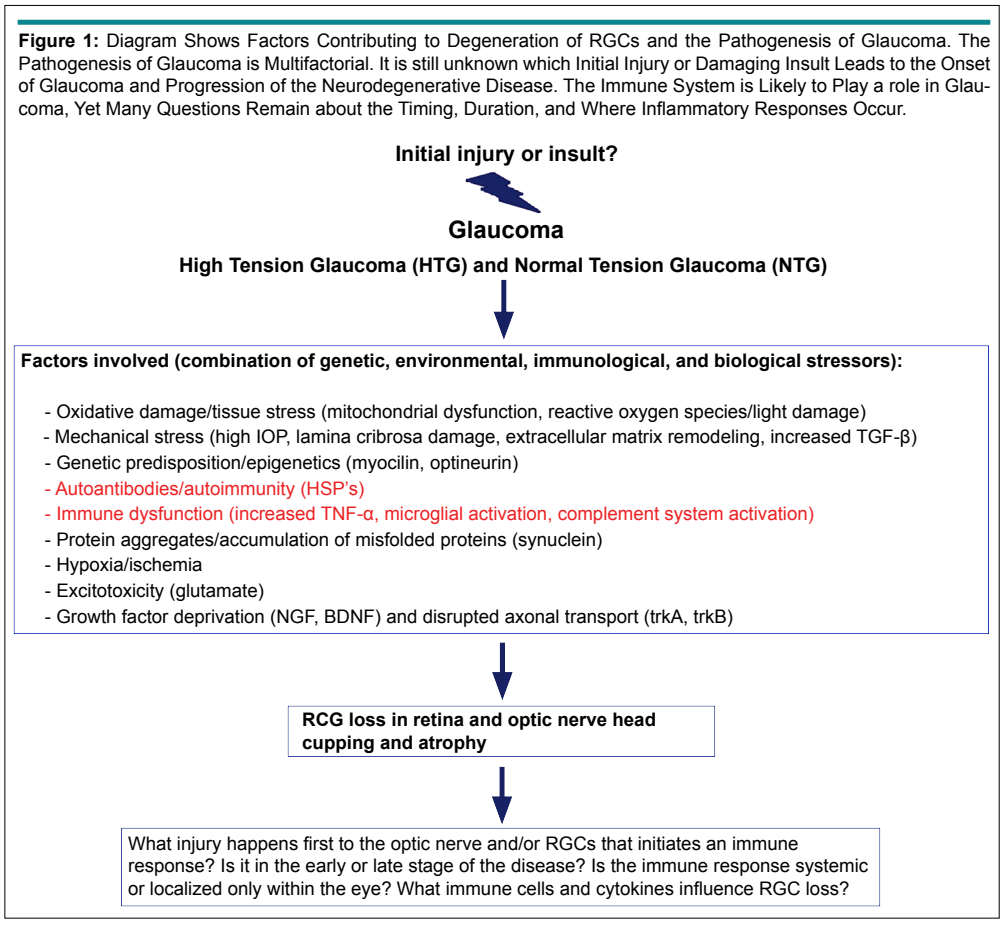

Figure 1: Diagram Shows Factors Contributing to Degeneration of RGCs and the Pathogenesis of Glaucoma. The Pathogenesis of Glaucoma is Multifactorial. It is still unknown which Initial Injury or Damaging Insult Leads to the Onset of Glaucoma and Progression of the Neurodegenerative Disease. The Immune System is Likely to Play a role in Glaucoma, Yet Many Questions Remain about the Timing, Duration, and Where Inflammatory Responses Occur.

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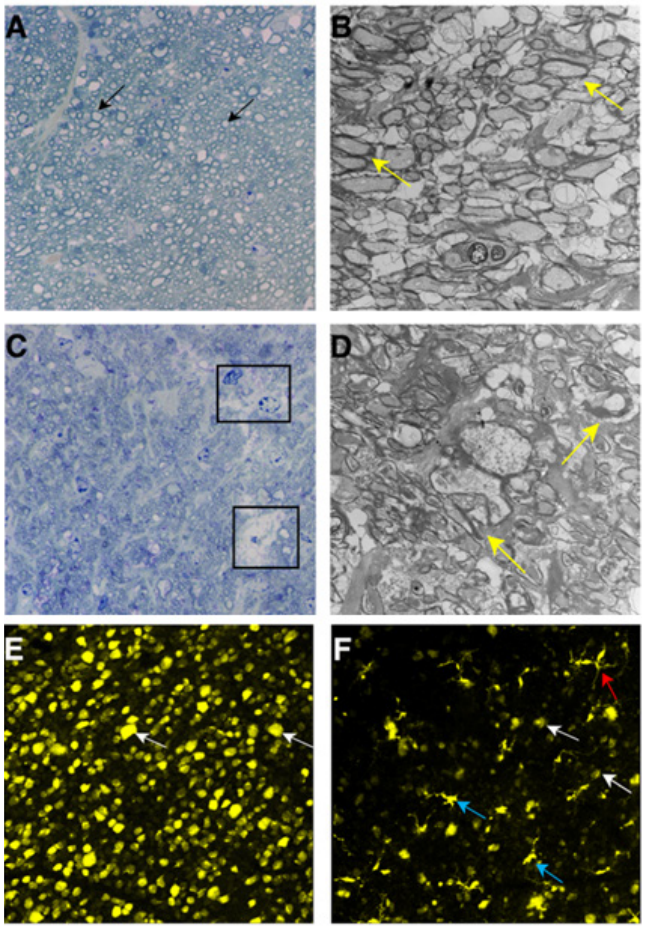
Low-level inflammation is important for biological homeostasis. Immune responses are necessary for proper tissue cleaning, maintenance, and repair.[19,20] It has also been proposed that protective or beneficial autoimmunity may help protect against neurodegeneration in the central nervous system (CNS).[11,21-25] This concept suggests that the immune system plays a key role in the ability of the CNS, like the optic nerve and retina, to withstand neurodegeneration, by recruiting both innate (resident and blood-borne macrophages) and adaptive (self-antigen specific T-cells) cells that together promote a protective niche and hinder disease progression under a well-controlled response.[23,24,26-29] However, excessively uncontrolled immune stimulation can lead to a neurotoxic environment in the optic nerve and retina, resulting in the neurodegeneration of RGCs. Immune dysregulation and immune activation in glaucoma pathogenesis are the focus of many studies in both experimental animal models and in human clinical studies.[14,20,30]

LIMITATIONS OF STUDYING IMMUNE RESPONSES IN EXPERIMENTAL GLAUCOMATOUS ANIMAL MODELS

Experimental glaucoma animal models are quite valuable.[31,32] They can be useful in studying the early changes in pathological and molecular changes in the optic nerve and retina. Since glaucoma is considered "the thief of sight" it can go undetected for many years in patients, making it hard to study in the clinic. Likewise, post-mortem eye tissue from human patients is typically limited to late onset and highly diseased glaucoma eyes, while early onset diseased eyes are not abundantly available for research studies. Studying glaucoma in humans is complicated; therefore, animal models are beneficial in dissecting out molecular mechanisms, especially for immune dysregulation and immune responses involved in the early stages of RGC injury.

There are several experimental animal models for glaucoma.[31,32] Some are based on chemical injury, such as intravitreal injection of neurotoxic concentrations of glutamate, while others utilize elevated pressure with laser injury to the trabecular meshwork or intravitreal injection of microbeads to raise IOP (injection of foreign beads into eye may not be an ideal glaucoma model to study immune responses). There are also animal models for mechanical-induced injury, where the optic nerve is transected or the optic nerve is crushed (Figure 2). Genetic models also exist such as the DBA/2J.[5] But all of these models have limitations, especially with studying immune system effects. No animal model can fully recapitulate human glaucoma due to its heterogeneous nature and each model can provide different insight into immune mechanisms and responses. The type of injury, whether biochemical or mechanical, may dictate a different immune response at a different time and location and may not only depend upon the severity, but also the chronicity of the injury. Moreover, some RGC cell types may be more susceptible to a particular injury; hence, certain RGCs may be more prone to immune attack or destruction than others. The immune responses are likely to be different in animal models, where IOP is experimentally raised *versus* in animals subjected to a non-pressure injury to the RGCs. Strain differences[33] can also influence a particular immune response due to differences in the major histocompatibility complex (MHC) and/or human leukocyte antigen (HLA) complexes. Animal models are important in studying immune responses associated with RGC injury and death, but teasing out significant correlations or trends between specific immune responses and RGC degeneration can be daunting, due to the inherent experimental variation present in animal models. Thus, translating the complex immune responses from glaucomatous animal models to human glaucoma is complicated for researchers, yet the immune system has been implicated in the pathogenesis of glaucoma.

Figure 2: Optic Nerve Crush Injury (ONC) is an Experimental Animal Model that Results in Axon Degeneration in the Optic Nerve and Retinal Ganglion Cell Loss.(A) Cross-section Stained with Toluidine Blue Showing a Normal Mouse Optic Nerve. The Black Arrows Depict Healthy Axons. (B) Transmission Electron Microscopy (TEM) Micrograph Illustrating Healthy Axons, which are Myelinated in a Normal Mouse Optic Nerve. (C) Cross-Section Stained with Toluidine Blue Showing a 4 Day Optic Nerve Crush Injured Mouse Nerve. The Black Boxes Represent Areas Where Axons have Undergone Loss and/or Degeneration. (D) TEM Micrograph Representing a 4 Day Optic Nerve Crush Injured Mouse Nerve. The Yellow Arrows Illustrate Sick and/or Dying Axons, which are Demyelinated. (E) Normal Mouse Retinal Flatmount with Fluoro-Gold Labeled RGCs. The White Arrows Show Healthy RGCs. (F) 4 Day Optic Nerve Crush Injured Mouse Retinal Flatmount with Dying RGCs. The Red Arrow Shows a Possible Astrocytic Glia Cell and the Blue Arrows Show Possible Microglia. The White Arrows Show Sick and/or Dying RGCs.



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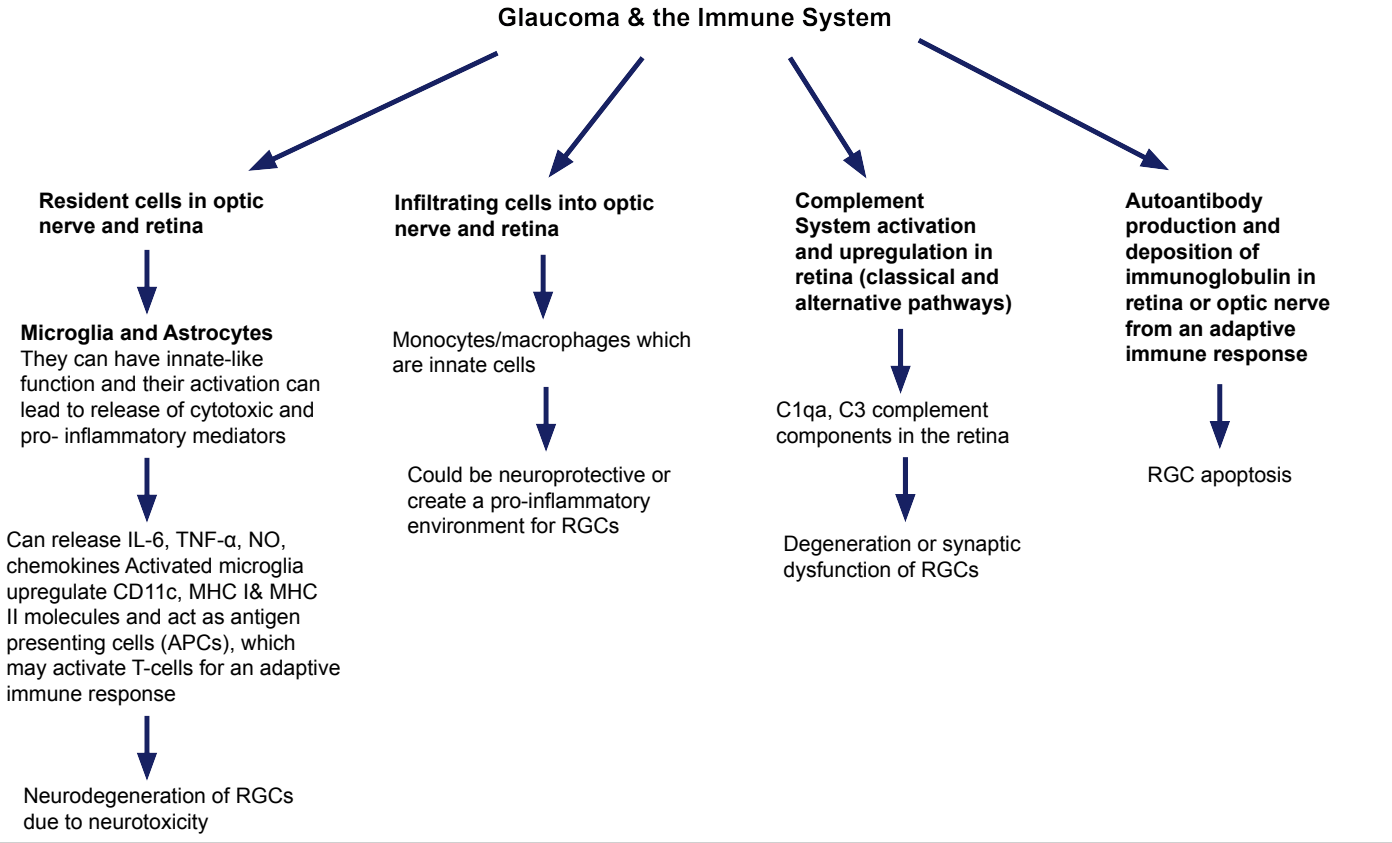
GLIAL INTERACTIONS IN GLAUCOMA

Many studies have shown immune cell responses are involved in glaucoma (Figure 3). This is especially true of glia (astrocytes and microglia), which are resident cells in the retina and optic nerve that can initiate an immune response.[19,34,35] Glia are important in immune surveillance, cleaning, as well as removing tissue debris. However, once astrocytes become reactive and microglia take on activated state, both cell types can increase production of cytokines (IL-6), reactive oxygen species (ROS), nitric oxide (NO), and tumor necrosis factor-α (TNF-α), creating a highly neurotoxic environment in the eye.[34,36] Microglia can express MHC molecules and function as resident antigen presenting cells.[34-36] It is possible microglia become dysregulated due to excessive activation in glaucoma. In the activated state, they recruit other immune cells leading to an uncontrolled adaptive immune response, resulting in increased antigenicity and increased antigen presentation. Microglia could be a therapeutic target and modulating their behavior in glaucoma may decrease RGC loss. Likewise, studying the interactions between RGCs and microglia may shed light on their tropic, cytokine, and immune cell interactions. There are over 20 types of RGCs and certain subtypes may interact more closely with microglia than others, which may influence their immune response to injury or stress.[30,37]

AUTOIMMUNITY AND GLAUCOMA

There is evidence that autoimmune mechanisms are involved in glaucoma.[1,2,17,18] Studies have shown the presence of autoantibodies against ocular antigens such a rhodopsin and glycosaminoglycans (GAGs).[1,7,38-40] It has been revealed that patients with normal tension glaucoma have increased levels of heat shock proteins, such as heat shock protein 60 (HSP 60), due to excessive tissue stress and damage.[17,18,41-43] But there is no direct evidence to confirm that RGC loss is due to humoral immunity in glaucoma. It is possible that retinal or optic nerve specific autoantigens are present in some glaucoma patients in a manner similar to organ specific autoantigens present in other autoimmune diseases. Autoantibodies in glaucoma patients may be generated as a secondary consequence to disease pathogenesis or they could be generated directly due to RGC death. Likewise, there is evidence aberrant immune activity glaucoma is due to molecular mimicry, through misguided immune responses to self-proteins resulting in injury. A host response is mistakenly directed at a self-protein because it shares high homology to a specific protein found on the surface of a pathogen, like a bacteria or virus.[17] One specific study showed increased *Heliobacter pylori* titers among glaucoma patients, which may represent molecular mimicry to this bacterium.[44] Furthermore, epitope mapping has revealed the immunogenicity of rhodopsin antibodies detected in glaucoma

Figure 3: Diagram Shows Possible Immune Factors Contributing to the Degeneration of RGCs. How the Innate and Adaptive Systems Contribute to Glaucoma, as well as Possible Autoimmune Responses, are Important Questions that Require Further Investigation. There are several Pro-inflammatory Factors that can Contribute to the Neurodegeneration of RGCs, which may be Possible Therapeutic Targets to Prevent or Delay RGC Loss in Glaucoma.



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patient sera is shared with epitope proteins found on common bacterial and viral pathogens.[14,17] Lastly, microbial flora whether oral, gastrointestinal, or ocular, may contribute to the pathogenesis of glaucoma.[45] Overall, autoimmunity may play a role in glaucoma, but it is still an area of open investigation.

COMPLEMENT PATHWAY AND GLAUCOMA

The complement system is a key pathway in the innate immune system. Various components in the complement system are upregulated in human glaucoma and in animal models of glaucoma.[15,46-49] The complement pathway can be activated in either the optic nerve head or in the inner plexiform layer of the retina.[20] It has been shown that RGCs sense damage or stress and respond by activating C1, which is part of the classical complement pathway. Once C1 is activated, C3 convertase is triggered by glial cells, which can amplify RGC damage by recruiting other immune cells like monocytes.[20,47] It is still unknown whether the complement pathway is directly responsible for RGC degeneration.

T-CELLS AND GLAUCOMA

Clinical studies have shown that glaucoma patients exhibit differences in immune cell populations, such as T-cells subsets.[3,34,50] A study showed significant alterations in Th1 and Th2 cytokine levels in human glaucoma patient serum.[50] In animal models, T-cell migration into the optic nerve has been observed. In immune deficient Rag1 knockout mice, which lack mature B- and T-cells, these mice have reduced RGC loss compared to immune competent wild type mice with experimental glaucoma injury.[3] But this has not been definitively shown in human glaucoma. T-cell migration into the human retina or optic nerve can be transient and it cannot be ruled out that T-cells can be cytotoxic to RGCs, even with short-term exposure of a small number of T-cells. There may be some type of systemic T-cell response to ocular stress from glaucoma that has yet to be fully unveiled.

NUMEROUS QUESTIONS STILL REMAIN ABOUT THE ROLE OF THE IMMUNE SYSTEM IN GLAUCOMA

Clearly, many unanswered questions remain about the role the immune system plays in glaucoma. First, the timing of the immune response, its duration (acute *vs*. chronic), and the severity of the immune response. Furthermore, the location of the insult, whether it is in the retina, optic nerve, or even the brain where RGCs project. Although, glaucoma is a disease of the optic nerve with loss of RGCs, it is still not clear where the injury occurs and what specific injury sets off an immune response and whether it is early or late in the disease process. Some have suggested the immune system plays a role in the progressive stages of the disease. But glaucoma pathogenesis involves both primary degeneration and secondary degeneration of RGCs. Primary degeneration occurs after the initial insult to the optic and/or retina, which leads to a chain reaction of cellular and cytokine responses, which creates a neurotoxic environment, resulting in secondary degeneration. The innate and adaptive immune systems are likely to have different roles and responses in the primary degeneration and secondary degeneration stages of glaucoma.

There are key areas in glaucoma research that require further development to study immune responses. For example, high contrast optical coherence tomography (OCT) imaging and adaptive optics imaging techniques of the optic nerve and retina can facilitate studying the role of the immune system in glaucoma patients. Additionally, studies are needed to determine which biomarkers or serum antigens can be indicators of glaucoma.[51] It has already been mentioned that HSP are autoantibodies found in glaucoma patients. It is likely there are other autoantibodies generated in response to tissue damage and stress.[10,52,53] Macrophages, have been shown to play a role in the pathogenesis of glaucoma, but whether they are protective or beneficial is still open for debate.[22,54,55] Identification of specific immune cells, whether they are pathogenic T-cells subsets or monocytes/macrophages may be prognostic indicators of disease progression.[56] Elucidation of epigenetic and genetic alterations, as well as age-related factors and susceptibility factors associated with glaucoma, is another area of open research inquiry.

In summary, glaucoma is likely a disease that is influenced by an uncontrollable immune response, due to an overwhelming burden of constant tissue insults. After a certain length of time and disease progression, the immune system may be unable to provide protection and only offer destruction to neurons. The question is how, when, and what specific immunotherapeutics, cellular therapies (stem cells), or immunomodulators can be used to slow or reduce the loss of RGCs and prevent disease progression, resulting in the precious preservation of sight in glaucoma patients.

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Mini Review

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Visual Processing Disorder in Children

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ABSTRACT

The minute persons think of eyesight, they generally think about accuracy, as in normal, 6/6 (or 20/20) vision. However, it is much more than that as the brain really processes the visual world, including things like symbols, pictures and distances. Faults in these brain tasks are called visual processing disorders (VPD) or visual processing issues. Many parents and teachers find it difficult to recognize the signs and symptoms of a VPD in their child or students. They also often confuse them with learning disabilities. This mini review aims to provide descriptions of visual processing issues and how to overcome through some vision, behavioral and education therapies.

KEY WORDS: Visual processing disorder (VPD); Learning disabilities; Behavioral therapies; Vision therapies.

INTRODUCTION

A visual processing disorder (VPD) is associated with the delayed capacity to perceive information received through the sense of vision. The symptoms of this medical condition are unlike the complications relating to eyesight or sharpness of vision. Problems with visual processing affects the interpretation and processing of the received visual information by the brain. For example, visual-spatial processing is the ability to define the spatial localization of objects. When a child passes the vision test during clinical examination but is unable to identify the differences between a triangle and a square, eyes are not responsible for this problem. The problem is essentially higher-processed visual skills.

Evidence suggests that the retina extends through the dorsal portion of the lateral geniculate nucleus of the thalamus to the primary visual cortex which is a tiny sheet of tissue, comparable in size to a half-dollar, situated in the occipital lobe in the posterior portion of the brain. The primary visual cortex is tightly packed with cells in several layers, just as is the retina. In its middle layer, which receives messages from the lateral geniculate nucleus, researchers have observed retorts alike to those seen in the retina and in the lateral geniculate cells.[1] Cells above and below this layer respond differently. For example, some of these cells may respond best to stimuli in the shape of bars or edges inclined at a certain angle. Further studies have suggested that different cells even prefer edges at different angles or edges moving in a particular direction. Though the visual processing mechanisms are not yet entirely implicit, current research undertaken by performing structural and physiological studies in monkeys suggest that visual signals are fed into at least three separate processing systems. One system appears to process the information mainly about shape; a second, mainly about color; and a third about the movement, location, and spatial organization.[1]

Visual processing issues are multifaceted. As there are eight diverse categories, and some individuals could show advanced symptoms of the condition than one. Hence, these concerns often go unobserved because they do not show up on visual or ocular examination. The various kinds of visual processing problems that the researchers have encountered in this domain have been listed as follows:

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Visual perception issues: Children experiencing this clinical condition have trouble visualizing the differences between two related letters, figures or objects. So there is a possibility that the patient may confuse between the letters, such as *d* and *b*, or *p* and *q*. We can improve the perception skills by giving hidden pictures, drawing, dot to dot, memory games and can also use developmental test for visual perception software to assess the skills in children from 4 to 12 years.

Visual figure-ground judgment issues: Children with this form of clinical concern may not be able to distinguish a contour or character from its contextual application. The patient might experience anxiety judging a detailed piece of evidence on a sheet. Activities like jigsaw puzzles, board games, find the odd one out, and sorting can be used for treatment. We also have standardized tests such as the test of visual perceptual skills (TVPS) that measure each of these skill areas based on a series of multiple choice line drawings. This test takes a bit longer to administer than some of the other occupational therapy testing because of the many sub-tests involved.

Visual sequencing issues: Children with related medical conditions struggle expressing the direction of signs, words or metaphors. They may tussle to inscribe responses on a single pane or miss lines during interpretation. They also may reverse or misinterpret letters, figures and words.

Visual-motor handling issues: Children with these problems have trouble expending a visual response to harmonize with a measure of the further parts of the body. Writing within the lines or margins can be tough. Children also may bump into things and have trouble copying from a book.

Long- or short-term visual memory issues: Children with either one form of visual memory concerns experience difficulty in recalling information they initially perceive. For this reason, they might have a problem with reading and spelling.

Visual-spatial issues: Children with these issues have trouble identifying the spatial localization of objects. This includes a misperception of the distance objects are from the observer and from each other. Also, identifying items and letters on paper or in a verbal description may be affected. These children may also have a difficult time reading charts and judging time.

Visual closure issues: Children with these issues have trouble detecting or recognizing an object when only portions of it are observable. For example, they cannot distinguish a car if its wheels are missing or an animal in a drawing that is missing a facial feature. Children may also perhaps experience great trouble with predicting context as they fail to identify a word if a letter is missing.

Letter and symbol reversal issues: Children with these issues tend to shift letters or numbers when writing or replace letters when reading after the age of seven years. Until approximately the age of seven years, reversals are normal. They also have a difficulty with letter or symbol construction that interrupts reading, writing and math abilities.

It is not clear as to how many children experience visual processing difficulties, but the symptoms often occur among children with learning disabilities.[2] Experts cannot state accurately the causes of these clinical issues, and they are often unaware that these effects are a consequence of the brain's inability to intercept and deliver visual signals received by the eyes. Certain studies recommend that low birth weight or extreme preterm birth can play a role.[3] It is also believed that minor traumatic brain injury could lead to visual processing issues, but then again there is no adequate evidences to completely support that concept.[4]

It is also very difficult to identify visual processing issues in children. Some of the symptoms arenot paying attention to visual tasks, getting easily distracted by too much visual information, being restless or inattentive during video or visual presentations, lacking interest in movies or television, etc.[5] Children may perhaps not express the signs of visual processing issues until they start school. However, the greater the length they drive lacking support, the better the influence may be on an extensive choice of abilities. When one observes a child facing difficulties in school, they should first send them for an eye exam and then consult to other specialists like pediatricians or neuropsychologists if there is no refractive or ocular disease concern.

What circumstances are associated with visual processing issues?

Visual processing problems do not constitute a learning disability in itself, but the symptoms often appear in children with reading, writing and math issues. Some specialists regard visual processing issues as threatening causes for learning issues such as dyslexia, but a comprehensive report from the American Academy of Pediatrics (AAP) states that visual processing issues are a result of that clinical condition, and not the cause.[5]

Treatment for visual processing issues

There are no medicines that can treat visual processing issues. However, if you think your child is also dealing with learning disabilities or other challenges like depression or anxiety, talk with the child's pediatrician and together, you can come up with a management plan for any co-occurring issues.

There are three kinds of therapies that are significant to be aware of as considering ways to help the child with visual processing issues: optometric vision therapy, behavioral vision therapy and educational therapy.[7]

Optometric vision therapy: It has been proven to help with vision problems that consist of eye movements or eye alignment. These

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eye coordination concerns are dissimilar from visual processing issues. Optometric vision therapy doesn't "cure" learning and attention issues. But if the child has vision problems in addition to dyslexia and other issues, solving vision problems can help him give more energy to result strategies that can help with the way the brain processes information.

Behavioral vision therapy: It is different from optometric vision therapy. Behavioral vision therapy involves eye exercises that are designed to improve visual perception. These eye exercises are also designed to improve visual processing skills. But there is no scientific study that shows this kind of therapy helps the brain process visual information.

Educational therapy: Teaches children strategies for working around their weaknesses. Learning how to approach problems can reduce frustration, increase self-confidence and lead to greater success in school. There are many non-medical ways parents and schools can help with visual processing issues in school and at home. Think of that learning can be multisensory. Children who have concern taking in visual information can be helped by hands-on activities as well as by listening.

Finally, this mini review concludes that with the right kind of strategies and support, children with visual processing issues can learn to read and write well. It is also a good idea to learn about assistive technology and adaptive tools as the more you comprehend about the child's problems, the easier it will be for them to find strategies that can help.

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Brief Research Report

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Writing Thank You Notes after Ophthalmology Residency Interviews?

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ABSTRACT

Objective: To determine the importance of writing thank you notes after ophthalmology residency interviews.
Design: Survey.
Participants: Ophthalmology residency faculty members.
Methods: A short multiple-choice survey using www.surveymonkey.com was distributed to Association of University Professors of Ophthalmology (AUPO) personnel who then distributed it to their respective faculty members that are involved in interviewing and ranking applicants. Six questions were asked to determine the importance of thank you notes after ophthalmology residency interviews along with the option to write comments.
Main outcome measures: The impact of thank you notes in the ranking of ophthalmology applicants following interviews.
Results: Seventy five total participants took the survey during the month of March 2016. Ninety point eight percent reported thank you notes never change their ranking of applicants; 4.6% responded yes, mostly in higher ranking; 4.6% responded yes, equally resulting in higher/lower ranking depending on the circumstances; and 0% chose yes, mostly resulting in lower ranking. When asked if they recommend applicants to write thank you notes: 46.7% chose no; 33.3% chose yes, only if personalized; 13.3% chose yes; and 6.7% chose yes, only if telling the program you are ranking them #1 (and mean it). Twenty six respondents wrote comments.
Conclusions: Based on the survey responses, largely thank you notes do not impact the ranking of ophthalmology applicants following interviews. However, many feel there is still a role for them.

KEY WORDS: Thank you notes; Ophthalmology residency interviews.

INTRODUCTION

The current gold standard is practicing evidence-based medicine. The road to residency is a rigorous one including 4 years of medical school, board exams, applying for residency, interviewing, and hopefully ending with matching at your desired program. What can and should one do after the interview?

Thank you notes after residency interviews remain to be recommended with only one survey done in 2010 asking 2 questions about thank you notes after ophthalmology residency interviews that revealed 14% of faculty members expect or desire them and only 3% are influenced by an applicant stating the program is their first choice.[1] Doing a quick Internet search, one can find numerous medical schools recommending thank you notes (UCSF, Drexel, Rutgers,and Iowa to name a few)[2-5] along with residency websites (American Academy of Family Practitioners and Emergency Medicine Residents Association)[6,7] and sites geared towards medical students.[8]

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METHODS

A 6 question multiple-choice survey was created using www.surveymonkey.com. The study was granted exempt status by the Institutional Review Board (IRB) of UT Health San Antonio. The survey was distributed to Association of University Professors of Ophthalmology (AUPO) personnel who then distributed it to their respective faculty members that interview and rank applicants. The survey included the following questions: the location of their residency program; their amount of time after training; do they enjoy receiving thank you notes; do thank you notes change their ranking of applicants; do they recommend applicants write thank you notes; and, if so, in what format. They were also allowed to write comments (See Supplementary Data).

RESULTS

Seventy five total people took the survey during the month of March 2016. Their location breakdown was the following: 35% Midwest, 35% Northeast, 9.5% West, 9.5% Southwest, 9.5% Southeast, and 1% anonymous. Fourty point three percent are faculty members for greater than 10 years, 29.2% faculty members less than 5 years, 19.4% residency directors, 8.33% faculty members for 5-10 years, and 2.8% chairmen. Twenty eight percent responded that they are indifferent to receiving thank you notes, 25.3% always enjoy receiving them, 25.3% enjoy them only if personalized, and 21% do not enjoy receiving them. Ninety point eight percent reported thank you notes never change their ranking of applicants (Figure 1); 4.6% responded yes, mostly in higher ranking; 4.6% responded yes, equally resulting in higher/lower ranking depending on the circumstances; and 0% chose yes, mostly resulting in lower ranking. When asked if they recommend applicants to write thank you notes: 46.7% chose no; 33.3% chose yes, only if personalized; 13.3% chose yes; and 6.7% chose yes, only if telling the program you are ranking them #1 (and mean it). Thirty seven percent do not have a preference between emailing thank you note *versus* hand-written, 21.9% prefer hand-written letters, 4.11% prefer email, and 37% responded non-applicable because do not recommend thank you notes. Twenty six respondents wrote comments at the end of the survey (Figure 2).

Figure 1: Do Thank You Notes Change the Ranking of Ophthalmology Applicants?

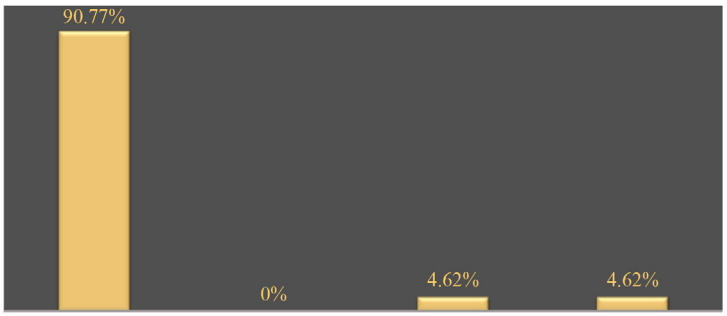

Figure 2A and 2B: Comments Provided by Survey Responders.

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DISCUSSION

Based on the comments, faculty members remain divided on the viewpoint of writing thank you notes after ophthalmology residency interviews. By in large, thank you notes do not appear to impact the ranking of ophthalmology applicants following interviews and are not seen as a requirement. They do, however, remain an option for an applicant to show their genuine interest in a program and an opportunity for a program to receive further insight into an applicant's personality.

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CONFLICTS OF INTEREST

Conflicts of interest only for Michael A. Singer: Allergan, Allegro, Ampio, Genentech, Ophthotech, Regeneron, Santen, Aerpio, Optos, Alcon, Clearside, Notal Vision, Guidepoint, Alimera.

In accordance with Openventio Publishers policy and my ethical obligation as a researcher, I am reporting that Dr. Singer is a consultant for the following companies: Allergan, Genentech, Regeneron, Santen, Clearside, Aerpio, and Alimera. Dr. Singer is a Speakers Bureau for the following: Allergan, Genentech, and Regeneron. Dr. Singer is involved in research support with the following: Allergan, Genentech, Regeneron, Ampio, Optos, Aerpio, Allegro, and Diachii, and Clearside. These affiliations did not affect research reported in the enclosed paper. I have disclosed those interests fully to Openventio Publishers.

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SUPPLEMENTARY DATA

Survey Questions

- Background Questions of Survey Responder:

1. Location of residency program: will provide a map of the United States so they can choose region of the United States (northeast, west, Midwest, southeast, southwest). There will also an anonymous option if they would rather not disclose location.

2. Number of years after training of the survey responder or Title (only can choose one option):

☐ Chairman
☐ Residency Director
☐ Faculty member for <5 years
☐ Faculty member for 5-10 years
☐ Faculty member for >10 years

- Specific Thank You Note Questions:

1. Do you enjoy receiving thank you notes:

☐ No
☐ Yes, always
☐ Only if personalized
☐ Indifferent

2. Do thank you notes change your ranking of applicants:

☐ Never
☐ Yes (if choose yes then will be given other options as below and a comment box at the end)
☐ Mostly only results in lower ranking (poorly written etc…)
☐ Mostly only results in raising ranking
☐ Equally results in raising or lowering ranking

3. Would you recommend applicants write thank you notes:

☐ Yes
☐ No
☐ Yes. Only recommend writing one to tell your #1 program that you are ranking them #1
☐ Yes, only if personalized

4. If said yes to #3, which format would you recommend?

☐ Email
☐ Hand-written on paper
☐ Either is fine
☐ N/A (not recommend)

Comment section at the end of the survey

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Case Study

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Baseline Visual Acuity of Women with Diabetic Macular Edema is Worse than Men: A Case-Control Study

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ABSTRACT

Purpose: To compare the baseline visual and anatomical parameters between the woman and men with diabetic macular edema (DME) who underwent intravitreal ranibizumab treatment.
Materials and Methods: This was a retrospective case-control study. Treatment naïve DME patients who were newly diagnosed and completed a follow time of 12 months in our clinic were included. All the patients were prescribed to receive a loading dose of three consecutive monthly injections. Then the patients were followed monthly, and treated on a pro-re-nata treatment regimen. Primary outcome measures of this study was the baseline best corrected visual acuity (BCVA) and central retinal thickness (CRT) in the female and male patients at the baseline. Secondary outcome measures were the change in BCVA and CRT during the 12 months follow-up period.
Results: Sixty-three eyes of 44 women, and 110 eyes of 76 men were included in the study. The mean baseline BCVA of the women was 0.72±0.44 (range 0.1-2.0) LogMAR, and the men was 0.49±0.31 (range 0.0-2.0) which was statistically significant between the two groups (p<0.0001). The mean baseline CRT of the women was 484±117 microns (range 312-759), and the men was 467±100 microns (range 320-704) (p=0.3). The mean visit number in women and men groups were 4.6±0.9 and 4.5±1.0, respectively (p=0.5). The mean injection number in women and men groups were 4.1±1.6 and 3.8±1.4, respectively (p=0.2).
Conclusion: Our results revealed that there may be a significant difference in baseline BCVA between women and men with DME at the first admittance. Perhaps we should be more sensitive in periodic ophthalmology consultations of women with DME and warn the general health care practitioners, internal medicine specialists and endocrinologists in this regard.

KEY WORDS: Diabetic macular edema; Gender; Ranibizumab.

ABBREVIATIONS: DME: Diabetic Macular Edema; BCVA: Best-Corrected Visual Acuity; CRT: Central Retinal Thickness; DR: Diabetic Retinopathy; DM: Diabetes Mellitus; anti-VEGF: anti-Vascular Endothelial Growth Factor; IVR: Intravitreal Ranibizumab.

INTRODUCTION

The metabolic diseases and especially the most frequent ones, type 2 diabetes mellitus (DM) and metabolic syndrome affect both genders.[1-4] Several studies were conducted to assess the relationship between the gender and end-organ damage of diabetes mellitus.[5-13] Previous studies investigated different organ systems and cardiovascular risk profiles, lipid profiles, risk of diabetic foot, risk factors for malignancy, and bone changes were evaluated in regard to gender difference in diabetic population.[6-12] Diabetic retinopathy (DR) is an important and devastating end-organ damage of DM which affects approximately one fifth of the patients after 20 years of disease duration.[14] Diabetic macular edema (DME) is the most frequent cause of visual loss in the patents with DR.[15-17] Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents are the most frequently preferred agents in the treatment of DME. Patients who were

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treated earlier with anti-VEGFs are likely to have better treatment outcomes.[17] In our daily practice, we realized that women with DME generally admitted later and with lower visual acuity than men.Therefore, in this study we aimed to compare the baseline visual and anatomical parameters between the female and male DME patients who underwent intravitreal ranibizumabtreatment.

METHODS

In this retrospective case-control study, medical records of the patients who had DME and underwent intravitreal ranibizumab (IVR) treatment between January 2013 and December 2015 in Istanbul Beyoglu Eye Training and Research Hospital were analyzed. Treatment naïve DME patients who were newly diagnosed and completed a follow time of 12 months in our clinic were included. The patients who were lost to follow-up in the first 12 months during our follow-up were not included. A written informed consent was obtained from all patients before the treatment. The study adhered to the tenets of the Declaration of Helsinki.

Data collected from the patients' records included age, gender, best corrected visual acuity (BCVA), central retinal thickness (CRT), and intraocular pressure (IOP) at the baseline, and at month 3, 6, 9, and 12. Visit and injection numbers during the first 12 months were also recorded. Patients were divided into two groups according to their genders and compared in regard to baseline and other parameters. Also the patients were divided into three groups in regards to baseline visual acuity and the gender groups were compared in regard to distribution of the patients into this three groups. Group 1 consisted of the patients with a baseline BCVA ≤1.0 logarithm of the minimum angle of resolution (LogMAR), group 2 consisted of the patients between 0.9 and 0.4 LogMAR, and group 3 consisted of the patients with a BCVA ≥0.3 LogMAR.

All patients underwent a standardized examination including measurement of BCVA *via* a projection chart at 4 meters, slit-lamp biomicroscopy, measurement of IOP *via* applanation tonometry, and biomicroscopic fundus examination. Fundus photography, fluorescein angiography (FA) (HRA-2; Heidelberg Engineering, Heidelberg, Germany), and optical coherence tomography (OCT) imaging (Spectralis; Heidelberg Engineering, Heidelberg, Germany) were performed before treatment. All examinations were repeated monthly, except for FA. Fluorescein angiography was repeated according to the physicians' discretion. Optical coherence tomography was used for detecting macular edema and measurement of CRT. Central retinal thickness, defined as the mean thickness of the neurosensory retina in a central 1 mm diameter area, was computed using OCT mapping software generated by the device. Diabetic macular edema was diagnosed *via* FA and OCT,and patients with a CRT of >300 microns were considered to have DME. The severity of DR, angiographic classification of DME, and ischemic status of macula were not assessed.

All injections were performed under sterile conditions after application of topical anesthesia, use of 10% povidone-iodine (Betadine; Purdue Pharma, Stamford, CT, USA) scrub was used on the lids and lashes, and 5% povidone-iodine was administered on the conjunctival sac. Intravitreal ranibizumab 0.5 mg/0.05 ml (Lucentis; Novartis, Basel, Switzerland) was injected through the pars plana at 3.5 mm posterior to the limbus with a 30 -gauge needle. Patients were instructed to admit back the hospital if they experienced decreased vision, eye pain, or any new arising symptoms.

Initially, all of the patients were prescribed to receive a loading dose of three consecutive monthly injections. Then the patients wereplanned to befollowed monthly, and a single injection of IVR was repeated when the BCVA decreased by one or more lines, or an increase of >100 microns in CRT in OCT images compared to the last visit, or disappearance of foveal pit compared to the last visit.

Primary outcome measures of this study were the baseline BCVA and CRT in the female and male patients. Secondary outcome measures were the change in BCVA and CRT during the 12 months follow-up period.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 20.0). Visual acuity was converted to the LogMAR for statistical analysis. Categorical variables were presented as numbers and percentages, while numerical variables were expressed as the mean and standard deviation. First the data was analyzed in terms of normality using Kolmogorov-Smirnov test. As the distribution of the data was found to be normal, the visual acuity and the CRT values between baseline and the other time points were assessed with repeated measures test. The means within the groups were compared using independent sample *t*-test. Categorical variables were compared using chi-square test. A p value <0.05 was considered statistically significant.

RESULTS

All of the included patients were Caucasians. Sixty-three eyes of 44 women, and 110 eyes of 76 men were included in the study. The mean age of the women were 59.2±8.2 (range 36-74 years), and men were 56.9±9.1 (range 26-79 years) (p=0.2). The other baseline characteristics were similar between the two groups (Table 1) (Figures 1 and 2).

The mean baseline BCVA of the women was 0.72±0.44 (range 0.1-2.0) LogMAR, and the men was 0.49±0.31 (range 0.0-2.0) which was statistically significant between the two groups (p<0.0001). In the women group 34.9% of the eyes (22 of 63) had a BCVA ≤1.0 LogMAR, whereas only 10.9% of the eyes (12 of 110) in the men group had a BCVA ≤1.0 LogMAR. The percentage of the patients with a visual acuity between 0.9

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Table 1: General Characteristics of the Patients.

	Women	Men	*p* value
Number of patients/eyes	44/63	76/110	-
Age (years)	59.2±8.2	56.9±9.1	0.2
Lens status (phakic/pseudophakic)	45/18	83/27	0.5
Baseline BCVA (LogMAR)	0.72±0.44	0.49±0.31	<0.0001
Baselne CRT (microns)	484±117	467±100	0.3

BCVA: Best Corrected Visual Acuiy; LogMAR: Logarithm of the Minimum Angle of Resolution; CRT: Central Retinal Thickness.

Figure 1: a) Fundus Photograph, b,c,d) Fluorescein Angiograms, and e) Optical Coherence Tomography Scan of a Women with Diffuse DME with a Baseline Visual Acuity of 1.3 LogMAR.

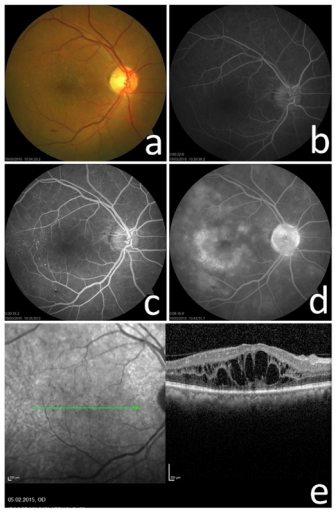
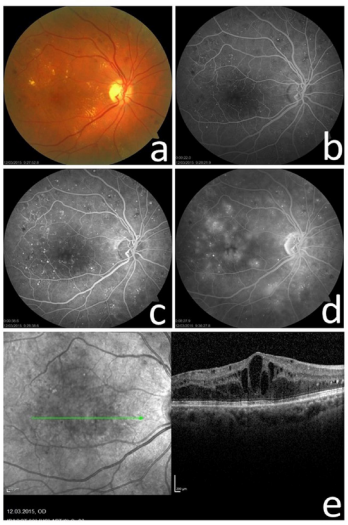


Figure 2: a) Fundus Photograph, b,c,d) Fluorescein Angiograms, and e) Optical Coherence Tomography Scan of a Men with Focal DME with a Baseline Visual Acuity of 0.5 LogMAR.



and 0.4 LogMAR was similar between the two groups and was 47.6% in the women and 52.7% in the men, respectively. The eyes with a BCVA ≥0.3 LogMAR compromised 17.5% (11 of the 63 eyes) of the women, and 36.4% (40 of the 110 eyes) of the men. The distribution of the BCVA groups between the two groups were statistically significant (p<0.0001). The mean BCVA levels of the two groups during the study period were summarized in Table 2. The change in mean BCVA was not statistically different between the two groups at any of the time points (p=0.4 for month 3, p=0.6 for month 6, p=0.6 for month 9, and p=0.08 for month 12, respectively).

Table 2. LogMAR Visual Acuity Values and CRT Findings in Microns in the Phakic and Pseudophakic Groups at Different Time Points.

Variables	Women	Men
Baseline visual acuity, mean	0.72±0.44 LogMAR (range 0.1-2.0)	0.49±0.31 LogMAR (range 0.0-2.0)
Month 3 visual acuity, mean	0.60±0.45 LogMAR (range 0.0-2.0)	0.46±0.38 LogMAR (range 0.0-2.0)
Month 6 visual acuity, mean	0.59±0.45 LogMAR (range 0.1-2.0)	0.39±0.30 LogMAR (range 0.0-1.3)
Month 9 visual acuity, mean	0.63±0.43 LogMAR (range 0.1-2.0)	0.37±0.32 LogMAR (range 0.0-1.3)
Month 12 visual acuity, mean	0.56±0.37 LogMAR (range 0.0-2.0)	0.42±0.32 LogMAR (range 0.0-1.3)
Baseline CRT, mean	484±117 µ (range 312-759)	467±100 µ (range 320-704)
Month 3 CRT, mean	394±113 µ (range 216-624)	392±108 µ (range 240-677)
Month 6 CRT, mean	364±116 µ (range 226-754)	366±82 µ (range 228-600)
Month 9 CRT, mean	403±154 µ (range 225-818)	355±88 µ (range 227-707)
Month 12 CRT, mean	359±127 µ (range 199-741)	373±109 µ (range 234-775)

CRT: Central Retinal Thickness; LogMAR: Logarithm of the Minimum Angle of Resolution; *vs.*: Versus; µ: Micrometers.

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The mean baseline CRT of the women was 484±117 microns (range 312-759), and the men was 467±100 microns (range 320-704) (p=0.3). The mean CRT levels of the two groups during the study period were summarized in table 2. The change in mean CRT was not statistically different between the two groups at any of the time points (p=0.9 for month 3, p=0.3 for month 6, p=0.3 for month 9, and p=0.2 for month 12, respectively).

The mean visit number in women and men groups were 4.6±0.9 and 4.5±1.0, respectively (p=0.5). The mean injection number in women and men groups were 4.1±1.6 and 3.8±1.4, respectively (p=0.2).

DISCUSSION

In this study we focused on an interesting topic which was the baseline BCVA levels of DME patients in regard to gender. Women seemed to admit to ophthalmologists with worse mean baseline visual acuity levels than men revealed by this study. The mean baseline BCVA of women was found to be 0.72 LogMAR and men was 0.49 LogMAR. The difference between the gender groups was 2.3 LogMAR lines. However, the mean baseline CRTand the other parameters during the follow-op period was similar between the two groups. The change in mean BCVA and CRT, along with the mean visit and injection numbers did not differ significantly. Different previous studies evaluated the relationship between the gender and other coexisting diseases with DM.[5-12] In a study by Al-Salameh et al, the association between gender and control of diabetes and other cardiovascular risk factors in patients with type 2 DM were investigated.[6] In the study it was revealed that women were less likely to be smokers or ex-smokers, and less likely to have cardiovascular disease at the baseline than men. During the follow-up period of 3 years mean hemoglobin A1C levels and blood pressure measurements were similar between the two genders, only low-density lipoprotein (LDL) cholesterol levels were wound to be significantly higher in women. Madsen et al, evaluated the gender differences in cardiovascular risk profiles of ischemic stroke patients with diabetes.[7] Of the assessed 3515 patients 1146 (33%) had DM. Among the several interpreted factors, no gender difference was found in patients with DM. However, it was reported that women with DM had strokes at a younger age. Self-efficacy in in diabetes self-management in type 1 DM patients was evaluated in a Danish population by Lindkvist et al.[11] The self-efficacy levels was assessed with a questionnaire between the adolescent girls and boys and the authors reported that the relationship between self-efficacy and age seemed to differ between girls and boys. Gamboa et al, evaluated the race and gender differences in statin use and LDL cholesterol control among the DM patients.[8] The recruited the patients with a LDL level >100 mg/dL, or were taking statins. In the study the authors divided the included patients into four groups which were white women, black women, white men, and black men, respectively. They reported that statin use was more frequent and LDL control was better in white women than the other three groups. Navarro-Paternella et al, conducted a cross-sectional trial regarding the differences between genders in relation to the factors which were associated with risk of diabetic foot in diabetic population.[9] They included 174 patients without a history of stroke or systemic vascular disease. In the study, it was reported that the risk factors associated with the development of diabetic foot were presented differently in female and male DM patients. The risk factors were reported to be older age, presence of calluses, and claw toes among women with DM, and were insulin use, presence of sensory comorbidities, ulcers, numbness, and stiffness in the feet among men. Dabrowski et al, evaluated the differences in risk factors of malignancy between men and women with type 2 DM in a retrospective multicenter study.[10] They reported that metformin use was associated with lower cancer risk in both genders. Breast and uterine cancer was the most prevalent malignancy among women and obesity and insulin treatment was associated with increased risk of cancer. Colorectal and prostate cancer was the most prevalent cancer among men. Patsch et al, investigated the interactions between gender and type 2 DM in regard to morphology of peripheral skeleton.[12] They concluded that skeletal hypertrophy was frequent in patients with DM, present in both genders with DM, and appeared attenuated at the tibial cortex in men. The gender differences in diabetic eye disease is assessed in two studies from Japan.[5,13] Kajiwara et al reported that among Japanese patients with DM, females exhibited a significantly higher prevalence of proliferative DR than men at baseline. Therefore they concluded that female gender was an independent risk factor for the development of DR.[5] In fact this study has a similarity to ours. Our women DME patients presented with lower BCVA levels than men and the women patients included in the study by Kajiwara et al more frequently presented with proliferative DR than the included men. The two findings, to present with more frequently with proliferative DR and with a lower visual acuity a baseline might both address a late admittance of women. We do not agree with the idea that female gender was accepted as an independent risk factor for the development of DR, because this might be solely secondary to the late admittance of women.In another study by Kamoi et al, risk factors for DME was evaluated and gender was not found to be associated with the risk of DME.[13]

In summary, interestingly diabetic women and men were not found to differ in regards to several discussed systemic disorders above. Also the control of diabetes and the prevalence of DR is known to be similar in both genders.[1-5] However, the baseline visual acuity levels were found to be significantly difference between women and men in our study. In addition the clinical course was similar and the change in mean BCVA and CRT was similar.

LIMITATIONS

The main limitation of this study was its retrospective design and relatively low sample size for this kind of study. However, this is the first study indicating a difference between women and men in regard to baseline parameters and reporting treatment outcomes of DME. Also all of the included patents were treat-

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ment naïve and first time admitters, which were other two strong properties of the study.

CONCLUSION

In conclusion, our results simply revealed that there may be a significant difference in baseline BCVA between women and men with DME at the first admittance. We suppose that women with DME admit to ophthalmologist lately than men, or at least they wait for a more prominent visual decrease. Perhaps we should be more sensitive in periodic ophthalmology consultations of women with DME.

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The study was in adherence to the Declaration of Helsinki, and consent forms were obtained from all of the patients before each treatment applied in the study. None of the authors have conflict of interest. All authors meet the requirements for authorship including substantive contributions, review and approval of the submitted work, and accept public responsibility for the final manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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