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The College of Ophthalmologists of Hong Kong

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- The *Hong Kong Journal of Ophthalmology* (HKJO) is the official publication of the College of Ophthalmologists of Hong Kong. The Journal aims to promote academic developments in ophthalmology, and to maintain continuing ophthalmological education of doctors of this specialty and other related disciplines. It is hoped that through achieving these aims, the quality of eyecare we offer to our patients can be lifted to new heights. The Journal will consider any submissions that fulfill these aims for publication.
- The Journal accepts high-quality submissions in the following categories: Original Article, Review, Perspective, Case Report, Photo Essay, Clinical Quiz, or Letter to the Editor. Editorials are by invitation only.
- The Journal is circulated to all members of the College of Ophthalmologists of Hong Kong and other professional societies and academic institutions in Hong Kong and internationally.

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香 港 眼 科 醫 學 院

THE HONG KONG JOURNAL OF OPHTHALMOLOGY
BEST ORIGINAL ARTICLE AWARD

Purpose

To encourage submissions to the *Hong Kong Journal of Ophthalmology* (HKJO) by trainees and fellows of the College of Ophthalmologists of Hong Kong (COHK).

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Two awards will be given out every year. Each awardee will be given a $2000 cash prize (HK dollars), which is supported generously by the Timothy KC Liu Fund.

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- Applicants must be a paid-up member or fellow of COHK at the time of submission.
- Trainees refer to those who have not been conferred the title 'FCOphthHK' at the time of submission.
- Only the first author of the article will be eligible for the prize. If the first author is not eligible for the award, i.e. not a member or fellow of COHK, then the order of consideration of awardee will be from the second author onwards to the last author.
- Original articles (including, but not limited to, prospective or retrospective clinical studies, observational studies, epidemiological studies, basic science studies, meta-analysis, etc) published in the HKJO during the year will automatically enter the selection process.
- Case reports (with case number <3), review articles and letters to the editor will not be eligible for this award.
- Submissions pending acceptance will not be eligible for the award.
- Entries will be based on the article as a unit, but not the author. Because of this, it is possible that one single author wins both awards, given that he/she is the first author of the two best original articles published that year (but he/she has to be a trainee in this case as one award is open for trainees only).

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- 1 representative from the University of Hong Kong
- 1 representative from the Chinese University of Hong Kong and
- President of the College

Selection Criteria

- Originality
- Scientific merit
- Methodology
- Presentation style

Award Presentation Ceremony

The awards will be given out at the following year's conferment ceremony.

Preparing *Hong Kong Journal of Ophthalmology* to apply for indexing next year

In this issue, Au et al[1] report on the outcomes of hyperbaric oxygen therapy (HBOT) for central retinal artery occlusion (CRAO) with symptom onset ≤6 hours after failed emergency bedside ocular treatment. Among 60 patients aged 27 to 89 years, the mean best-corrected visual acuity (BCVA) improved from 2.02±0.36 (range, 0.7-3.0) logMAR (Snellen equivalent to around hand movement) to 1.53±0.61 (range, 0.1-3.0) logMAR (Snellen equivalent to 20/640), with an improvement of 0.49±0.57 logMAR (p<0.00001). 39 (65%) eyes had improvement, whereas 20 (33.3%) eyes had no improvement and one eye had a decrease in BCVA. Given BCVA of light perception or worse cannot be accurately converted to LogMAR, the authors excluded 15 such patients. Further analysis of the remaining 45 patients showed that the mean BCVA improved from 1.87±0.25 (range, 0.7-2.0) logMAR (Snellen equivalent to 20/1400) to 1.41±0.63 (range, 0.1-2.0) logMAR (Snellen equivalent to 20/500), with an improvement of 0.47±0.63 logMAR (p<0.00001). Although the improvement of BCVA after HBOT is significant, readers may doubt whether Snellen equivalence of 20/640 in the overall group and 20/500 in the subgroup is clinically significant and better than the natural history of untreated eye. In a prospective study on the natural history of visual outcome assessed by fluorescein fundus angiography in patients with CRAO, significant improvement in vision can occur without treatment in certain eyes, and the visual outcomes are highly varied.[2] Conversion of the Snellen chart to logMAR may be arbitrary and inaccurate not only for light perception and no light perception but also for finger counting and hand movement. Various conversions are recommended.[3] It would be interesting to further analyze the subgroup that exclude eyes with poor visual acuities. Ideally, a randomized controlled study comparing treated and untreated eyes with CRAO of the same type may provide more guidance.

We are working closely with the Hong Kong Academy of Medicine (HKAM) Press to prepare the *Hong Kong Journal of Ophthalmology* for indexing next year. Key issues that we are dealing with include: applying for ISSN for the online version, adding Editorial Office staff and Publisher (HKAM Press) information to 'Editorial Team' page in the website, and adding information for advertisers. We would also like to adopt a 'continuous online publication' model whereby papers are published online soon after acceptance. For the time being, the print version would still be published in June and December each year.

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ORIGINAL ARTICLE

Efficacy and safety of hyperbaric oxygen therapy for acute central retinal artery occlusion in Hong Kong: results of the first 3 years

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Abstract

Purpose: To review the efficacy and safety of hyperbaric oxygen therapy (HBOT) for central retinal artery occlusion (CRAO) in Hong Kong patients.
Methods: Patients diagnosed with CRAO with symptom onset ≤6 hours who failed emergency bedside ocular treatment were referred to a course of HBOT. Changes in best-corrected visual acuity (VA) after HBOT and adverse effects and complications of HBOT were recorded. Changes in best-corrected VA between the pre-COVID-19 group and the COVID-19-pandemic group were compared.
Results: 34 men and 26 women with CRAO aged 27 to 89 years were included for analysis. The mean follow-up period was 169±226 days. The mean number of HBOT sessions received was 8.6±3.2. The mean best-corrected VA improved from 2.02±0.36 to 1.53±0.61 logMAR after HBOT (p<0.00001). 65% of patients had improvement and 33.3% had no improvement. VA changes between the pre-COVID-19 group (n=22) and COVID-19-pandemic group (n=38) were comparable (-0.53±0.58 vs -0.46±0.57 logMAR, p=0.59), despite a delay in hospital attendance. 41.7% of patients failed to equalize the pressure during treatment requiring myringotomy or even grommet insertion. 20% of patients had barotrauma. Other adverse events included convulsion, confusion, sinus pain, and hypoglycemia.
Conclusion: In patients with CRAO, HBOT may be effective in improving best-corrected VA, even during the COVID-19 pandemic.

Key words: COVID-19; Hyperbaric Oxygenation; Retina; Retinal artery occlusion

Introduction

Central retinal artery occlusion (CRAO), also known as ocular stroke, is an ophthalmic emergency that may cause blindness.[1,2] Managements for CRAO include breathing into a paper bag, carbogen inhalation,[3] topical and/or systemic medical treatment for lowering intraocular pressures, ocular massage, anterior chamber paracentesis,[4] or even thrombolytic therapy.[5] Nonetheless, there is no consensus on the gold standard management.[6]

In Hong Kong, hyperbaric oxygen therapy (HBOT)[7] for CRAO was started in November 2018 at the Pamela Youde Nethersole Eastern Hospital,[8] which receives referrals from both public and private practitioners 24 hours every day,[9] even during the COVID-19 pandemic.[10] We have previously reported an absence of SARS-CoV-2 among our cohort and delayed hospital presentation during the COVID-19 pandemic.[11-13] This study aims to review the efficacy and safety of HBOT for CRAO in Hong Kong patients.

Methods

Patients diagnosed with CRAO with symptom onset ≤6 hours who failed emergency bedside ocular treatment were referred to a course of HBOT. Patients with iatrogenic CRAO secondary to cosmetic facial filler injection, neurosurgical interventional radiology procedures, or intraarterial chemotherapy injection were excluded, as were those who presented beyond the 6-hour timeframe or had contraindications of HBOT such as untreated pneumothorax or bleomycin usage.

Patients underwent slit lamp and dilated fundus examinations to confirm the diagnosis, and their visual acuity (VA) and intraocular pressure were measured. Eyes with pathologies other than CRAO were excluded from HBOT. Patients with acute visual loss arising from branch retinal artery occlusion (BRAO) or cilioretinal artery occlusion were excluded, although evidence supporting HBOT to treat BRAO is increasing.[14] Patients were treated by a multidisciplinary team of internal medicine physicians and emergency department HBOT practitioners.

Patient data (age, sex, ethnicity, follow-up duration, onset-to-door time, diseased eye laterality, best-corrected VA, past ophthalmic history, past medical and drug history) were retrieved from the electronic health record system of the Hospital Authority.[15] The best-corrected VA was measured on the Snellen charts and converted to the logarithm of minimal angle of resolution (logMAR) units for analysis,[16] with finger count=1.7 logMAR, hand movement=2.0 logMAR, light perception=2.3 logMAR, and no light perception=3.0 logMAR.

The primary outcome was the VA changes after HBOT. Secondary outcomes were adverse effects and complications of HBOT. As there was a delay in hospital presentation during the COVID-19 pandemic,[13] the pre-COVID-19 group (before 23 January 2020 when the first confirmed COVID-19 case was recorded in Hong Kong) was compared with the COVID-19-pandemic group to determine the difference in VA changes. Normality of data distribution was tested by the Shapiro-Wilk test.[17] Statistical analysis was performed using the SPSS (version 27, IBM, Armonk [NY], USA).

Results

As of 30 November 2021, 70 patients who required an emergency call for HBOT were identified. 10 patients were excluded owing to ophthalmic artery occlusion from internal carotid artery pathologies such as carotid artery dissection from hypertension (n=1) and carotid artery stenosis from previous radiotherapy for nasopharyngeal cancer (n=1) as well as non-CRAO cases such as BRAO, retrobulbar optic neuritis, orbital apex tumor, and central serous chorioretinopathy (n=8).

34 men and 26 women with CRAO aged 27 to 89 (mean, 67.5±14.4) years were included for analysis. 31 left eyes and 29 right eyes were involved; no patient had bilateral presentation. The mean follow-up period was 169±226 (range, 4-912) days. The mean number of HBOT sessions received was 8.6±3.2 (range, 1-10). The mean best-corrected VA improved from 2.02±0.36 (range, 0.7-3.0) logMAR (Snellen equivalent to around hand movement) pre-HBOT to 1.53±0.61 (range, 0.1-3.0) logMAR (Snellen equivalent to 20/640) after treatment (p<0.00001), with an improvement of 0.49±0.57 logMAR. 39 (65%) eyes had improvement, 20 (33.3%) eyes had no improvement, and one eye had a decrease in VA.

Given VA of light perception or worse cannot be accurately converted to LogMAR, 15 such patients were excluded. In the remaining 45 patients, the mean best-corrected VA improved from 1.87±0.25 (range, 0.7-2.0) logMAR pre-HBOT (Snellen equivalent to 20/1400) to 1.41±0.63 (range, 0.1-2.0) logMAR (Snellen equivalent to 20/500) after treatment (p<0.00001), with an improvement of 0.47±0.63 logMAR.

VA changes between the pre-COVID-19 group (n=22) and COVID-19-pandemic group (n=38) were comparable (-0.53±0.58 vs -0.46±0.57 logMAR, p=0.59).

No patient had CRAO in the contralateral eye during the follow-up period. Two patients had cerebrovascular stroke shortly after the diagnosis of CRAO, and HBOT was terminated after one or two sessions for the treatment of stroke. The first patient had left common carotid artery atherosclerosis, and CRAO was the first presentation before the full presentation of middle cerebral artery stroke 1 day later. The patient required thrombectomy subsequently. The second patient was 45 years old and had right lateral dorsal pontine lacunar infarct, and was later found to have hypertension, hyperlipidemia, and moderate obstructive sleep apnea. 33 (55%) patients had adverse events including failure to equalize the pressure during treatment requiring myringotomy or even grommet insertion (n=25), barotrauma of grade 1 to 3 (based on the modified Teed Classification[18]) but without any perforation (n=12), convulsion secondary to oxygen toxicity (during the first session while decompressing from 180 kPa to 139 kPa at 94 minutes) [n=1], confusion with agitation and aggressive behavior (n=1), sinus pain (n=1), and shortness of breath (n=1). Three patients had hypoglycemia; two of them had diabetes mellitus.

Discussion

In the present study, the best-corrected VA improved significantly after HBOT, which is consistent with a case series of 128 patients that reported a mean VA improvement from 2.14±0.50 logMAR (Snellen equivalent to hand movement) to 1.61±0.78 logMAR (Snellen equivalent to 20/800) [p<0.0001].[19] To the best of our knowledge, the present study includes the largest case series of Chinese/Asian patients on visual outcomes of HBOT for CRAO.

The incidence of ischemic stroke within 15 days of CRAO

has been reported to range from 2.2% to 5.3%,[20-22] which is similar to the 3.3% among our cohorts. None of our patients had hemorrhagic stroke. However, occurrence of transient ischemic attack around CRAO was not recorded. In Chinese patients with retinal artery occlusion, the stroke risk was 2.07 times higher than controls.[23]

Middle ear barotrauma is a common adverse effect of HBOT, with incidence ranging from 9.2% to 66.7%.[24,25] 20% of our patients had barotrauma; all were older than 55 years except one. Female sex and age >55 years are risk factors.[26] Hypoglycemia is a complication of HBOT and can precipitate other neurological complications. HBOT can decrease blood glucose level even on healthy subjects.[27] The incidence of hypoglycemia during or immediately after HBOT is 1.5% (range, 0.8%-2.1%).[28] One of the three patients with hypoglycemia did not have diabetes mellitus. There is evidence suggesting a reduction in glycemia following HBOT in patients with diabetes mellitus, but the sample size is small and potentially underpowered.[29]

There are a few limitations to the study. Only subjects with symptoms onset of ≤6 hours were included, and thus many patients were unable to benefit from HBOT, although the Undersea and Hyperbaric Medical Society recommends HBOT within 24 hours of symptoms onset.[30] In most patients, HBOT were initiated before the serological investigation results were available, particularly results of the erythrocyte sedimentation rate were only available during office hours. Thus, patients with arteritic CRAO may have been included, despite the low prevalence of giant cell arteritis in Chinese populations.[31] Such patients are known to have poor visual outcomes. During the COVID-19 pandemic, hospital attendance patterns changed drastically.[32] Despite this, the pre-COVID-19 group and the COVID-19-pandemic group were comparable in terms of VA improvement. There was no comparative arm to determine the efficacy of HBOT for CRAO. Randomized studies comparing HBOT with conservative treatment for CRAO are warranted.

Conclusions

In patients with CRAO, HBOT may be effective in improving best-corrected VA, even during the COVID-19 pandemic.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

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REVIEW ARTICLE

Gene therapies for retinal dystrophies: potential in the Chinese population

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Abstract

Retinal dystrophies (RD) refer to a group of clinically and genetically heterogenous degenerative conditions of the retina. We aim to summarize emerging gene therapies for RD and their efficacy in restoring photoreceptor or bipolar cell functions. In patients with retinitis pigmentosa, injection of adeno-associated virus containing *RPE65*, *RPGR* or *MERTK* results in improvements in outcomes of the multi-luminal mobility test and full-field light sensitivity threshold test. In animal models of congenital stationary night blindness, gene augmentation of *Cacn1f*, *LRIT3* or *Nyx* increases ON-bipolar cell signaling cascade and preserves retinal morphology. Patients with achromatopsia show improved visual acuity, contrast sensitivity, and cone responses after injection of a vector comprising *CNGA3* or *CNGB3*. In patients with Leber congenital amaurosis, administration of a vector containing *RPE65* or *RDH12* results in improved full-field sensitivity to white light and photoreceptors responses, particularly in pediatric populations. Some patients have improved dark-adapted spectral sensitivities and pupillary light responses after injection of vectors. For choroideremia, *REP1* gene therapy has been shown to improve visual acuity and retinal sensitivity. Nonetheless, voretigene neparvovec-ryzl (Luxturna) remains to be the only approved gene therapy in patients with biallelic *RPE65* mutation. In the Chinese population, *RPGR*, *Lrit3*, *Nyx*, *CNGA3*, *RPE65*, *RDH12*, and *CHM* gene therapies may be beneficial, because the mutated genes are compatible with the genes investigated in previous clinical trials. A thorough understanding of gene therapies for different RD subtypes may allow more personalized management of retinal degeneration.

Key words: Choroideremia; Color vision defects; Gene therapy; Leber congenital amaurosis; Night blindness, congenital stationary; Retinitis pigmentosa

Introduction

Retinal dystrophies (RD) refer to a group of clinically and genetically heterogenous degenerative conditions of the retina. RD have a prevalence of 1 in 4000 and affect >2 million people wordwide.[1,2] RD may be inherited with an autosomal dominant, autosomal recessive, or X-linked mode, whereas some cases may be sporadic in nature.[3] Disease onset varies from neonatal to early adolescence or adulthood. Clinical presentations range from poor peripheral or dim vision and tunnel vision to complete blindness, depending on the gene affected and the disease severity.[3] Visual impairment is associated with reduced independence, resulting in mental and financial burden.[4]

The retina consists of photoreceptors, mainly rod and cone cells, which are reactive to dim and bright light, respectively. Light signals are then phototransduced into electric signals, which are sent via the optic nerve to the occipital lobe of the central nervous system for image processing.[5] Phototransduction requires the integrity of retinal pigmental epithelium (RPE), a single layer found below

the photoreceptors. RPE stores nutrients for photoreceptors and phagocytoses, the oldest portion of photoreceptor outer segment. RPE is the main site of vitamin A storage, which helps the isomerization of retinoids in the classical visual cycle.[6] 11-*cis*-retinal first bounds to cone opsins or rhodopsin, which is then photoisomerized to all-*trans*-retinal. All-*trans*-retinal is then reduced to all-*trans*-retinol and transported to RPE. Inside RPE, an enzyme RPE65 is responsible for the *trans*-to-*cis* isomerization to regenerate the visual chromophore.[7] The underlying cause of RD can be attributed to >270 genes involved in the retinoid cycle, photoreceptor survival, and phototransduction.[8] Depending on the cell types involved, RD can be classified into different phenotypes such as rod-dominated disease (retinitis pigmentosa [RP], congenital stationary night blindness [CSNB]), cone-dominated disease (achromatopsia), generalized retinal degeneration involving both cells (Leber congenital amaurosis [LCA] and choroideremia), and vitreoretinopathies.[3]

Currently, there is no effective treatment for RD. However, gene therapies have shown to restore vision and cell-based therapies (embryonic stem cells, induced pluripotent stem cells, and retinal progenitor cells) have been performed in mouse models.[9-11] Gene therapy uses exogenous DNA to treat genetically mutated disease.[12] It has been applied to retinal pathologies; the therapeutic amount requirement is small, and the presence of the blood-retinal barrier helps avoid immunological responses.[1]

We aim to review the emerging gene therapies for RD (RP, CSNB, achromatopsia, LCA, and choroideremia) and their effectiveness in preserving vision. The gene defects found in Chinese patients with RD and the potential use of gene therapies for such patients are also discussed.

Rod-dominated diseases

Retinitis pigmentosa

RP is the most common subtype of RD. RP results in loss of rods and subsequently cones and RPE functions. RP involves the mutations of *RHO*, *ROM1*, *PRPH2*, and *RPE65*.[13] Patients with RP first manifest with nyctalopia, followed by a loss of peripheral vision and eventually blindness. Subretinal injection of adeno-associated virus (AAV)–carrying genes that affect RP including AAV2-hRPE65, AAV8.coRPGR, and rAAV2-VMD2-hMERTK has been reported to improve rod functions in clinical trials (**Table 1**).

AAV2-hRPE65v2

RPE65 gene encodes all-*trans* retinyl ester isomerase that helps the conversion into 11-*cis*-retinol in the visual cycle for chromophore regeneration and phototransduction.[13] In a phase 1 trial of 11 individuals with *RPE65* mutations,[14] unilateral subretinal injection of voretigene neparvovec (AAV2-hRPE65v2), an AAV2 vector containing human RPE65 cDNA, resulted in a robust improvement in the functions of rods and cones (measured by full-field light sensitivity threshold [FST] testing) at day 30 and until 3 years ($p<0.0001$ for all timepoints). Six patients had increased sensitivity to white and blue light by at least 10 dB. Nonetheless, no clinically significant improvement in visual acuity was reported, although no adverse event was reported either.

In a phase 3 trial of 31 patients with biallelic *RPE65* gene mutation who were randomized to receive placebo or subretinal injection of voretigene neparvovec in the worse-seeing eye for 1 year,[15] the intervention group showed higher improvement in the bilateral multi-luminance mobility test (MLMT) mean score (1.8 vs 0.2), improvement of a mean of >2 log units in the FST testing by day 30 ($p=0.0004$) and until 1 year, higher improvement in mean LogMAR (8.1 vs 1.6 letters), and doubling of the mean sum total degrees of Goldmann visual field (compared with a decrease in the control group).

In 29 patients with *RPE65* mutation in a phase 1 follow-up study at year 4 and a phase 3 study at year 2,[16] unilateral subretinal injection of voretigene neparvovec-ryzl (AAV2-hRPE65v2) resulted in an improvement in the mean MLMT lux score at day 30 and the score remained stable over 4 years (2.4 at 4 years, 1.9 at 2 years, and 2.1 at 1 year), compared with 0.2 in the control group ($p=0.004$) and an improvement in the mean white light FST at 1 year, with a gain of >2.3 $\log^{10}$ units. All patients with an increase of the MLMT score of 1 had FST improvement. Seven of 11 patients who had MLMT improved by 1 light score achieved maximum lux score, which reflects the ceiling effect of MLMT score at minimal measurable light level.

In a phase 3 randomized controlled trial of 31 patients with biallelic *RPE65* mutation who received subretinal injection of voretigene neparvovec in both eyes,[17] the improvement in the MLMT score in both eyes was 1.8 at year 3 and 1.7 at year 4. 71% of patients were able to pass MLMT at the lowest light level at year 3. The mean change in FST was -2.04 $\log_{10}$ (cd.s/m^2) at year 3 and -1.90 $\log_{10}$ (cd.s/m^2) at year 4. There was a clinically significant improvement of visual acuity of binocular vision by ≥-0.3 logMAR at year 3.

In six pediatric patients with biallelic *RPE65* mutation who received subretinal injection of rAAV2-CB-hRPE65 in the worse-seeing eye,[18] four patients had improvement in visual acuity during the first 2 years and until subsequent years. Two of them had improved visual acuity in the untreated eye as well. Four patients had no change in the V4e target from the normal baseline, whereas three patients had no change in visual field or III4e or II4e targets based on the kinetic perimetry. Despite that, three patients showed improved central 30° and total hill of vision in the treated eye based on static perimetry during the first 2 years. However, five adult patients in the same study showed no significant improvement in visual acuity or static perimetry. This demonstrates the effectiveness of gene therapy in the pediatric group in improving visual acuity and visual field.

Table 1. Gene therapies for retinitis pigmentosa

Study	Country	Gene mutated	Groups and sample size	Parameters	Main results
AAV2-hRPE65v2					
Bennett et al, 2016[14]	United States	*RPE65*	11 patients with *RPE65* mutation had subretinal administration of AAV2-hRPE65v2 in one eye, followed up for 3 years.	Goldmann visual field test, full-field light sensitivity threshold testing, white, blue and red stimuli, visual acuity.	Visual field tests showed islands of responding retina and expansion of visual field by day 30 corresponded to injection area. Full-field light sensitivity threshold testing showed improvement in rod and cone function by day 30.
Russell et al, 2017[15]	United States	*RPE65*	31 patients with biallelic *RPE65* mutations divided into intervention group with subretinal injection of voretigene neparvovec for 1 year or control group (2:1).	Multi-luminance mobility testing performance, full-field light sensitivity threshold, BCVA, visual field.	Intervention group had mean bilateral MLMT change of 1.8 while that of control group was 0.2. No control patients passed MLMT at the lowest luminance level but 65% of the intervention group passed it. Mean full-field light sensitivity threshold in the group with gene therapy had a rapid and greater improvement by day 30.
Maguire et al, 2019[16]	United States	*RPE65*	29 *RPE65*- mutated subjects with 20 having bilateral subretinal injection of vector and 9 serving as control group.	Change in performance on multi-luminance mobility test, full-field light sensitivity threshold, BCVA, visual field.	Mean MLMT lux score showed improvement by day 30 visit and remained stable for 4 years in the interventional group. 72% of the patients passed MLMT at the lowest illuminance level. Mean full-field light sensitivity threshold improved at 1 year.
Maguire et al, 2021[17]	United States	*RPE65*	31 patients with *RPE65* mutation randomized 2:1 to intervention with voretigene neparvovec subretinal injection or control.	Multiluminance mobility test, full-field light sensitivity threshold white light, visual field, visual acuity.	Mean MLMT at year 4 for intervention group was 1.7 and that of control group was 2.4, having 71% of patients being able to pass MLMT at the lowest light level. Full-field light sensitivity threshold white light showed a mean change of -2.04 log10 and -2.91 log10 in interventional and control group respectively.
Pennesi et al, 2018[18]	United States	*RPE65*	11 subjects with *RPE65* mutation received rAAV2-CB-hRPE65 subretinal injection in the worse-seeing eye, followed up for 5 years.	BCVA, static perimetry hill of vision measurements, kinetic perimetry, visual field area.	Paediatric patients showed improved BCVA and static perimetry results but not in the kinetic perimetry. Adult subjects had no consistent changes in the parameters measured.
AAV8.coRPGR					
Cehajic-Kapetanovic et al, 2020[19]	United Kingdom and United States	*RPGR*	18 patients with *RPGR* gene mutation received subretinal AAV8. *coRPGR*, another eye as the fellow eye.	Visual acuity, microperimetry, central corneal thickness.	VA returned to baseline by 3 months post-treatment. Mean visual field change was +0.5 dB in treated eye while that in control eye was +0.1 dB.
rAAV2-VMD2-hMERTK					
Ghazi et al, 2016[21]	Saudi Arabia	*MERTK*	6 patients with *MERTK*-related RP received subretinal injection of rAAV2-VMD2-hMERTK for 2- year follow up.	BCVA, intraocular pressure, full-field stimulus threshold test.	50% of the patients showed improved visual acuity in the treated eye. No significant difference in mean FST values between operated and non-operated eyes.

AAV8. coRPGR

RP GTPase regulator (*RPGR*) gene mutation is associated with X-linked RP. In the first phase 1 and 2 trials of 18 patients with genetically confirmed variants in *RPGR* who were randomized to receive subretinal injection of codon-optimized serotype 8 vector (AAV8. coRPGR) in three different concentrations,[19] six patients with mid-dose (5×10^{11} gp/mL) achieved an improvement in retinal sensitivity and visual field at month 1, which persisted to month 6. The mean change in microperimetry at month 6 was +0.5 dB in treated eyes and +0.1 dB in untreated eyes. The mean change of LogMAR was -0.1 letters in treated eyes and +0.8 letters in untreated eyes; the treated eyes had less improvement because the outcome of gene therapy involves the interplay of neurodegeneration, vector dosage, and injection-related inflammation in the early phase. Foveal central retinal thickness revealed a decrease of 10.8 μm in treated eyes and 10.9 μm in untreated eyes. Optical coherence tomography showed similar retinal morphology. These findings suggest that gene therapy preserves the degeneration of the outer retinal structure.

rAAV2-VMD2-hMERTK

MER proto-oncogene, tyrosine kinase (MERTK) gene

involves in the phagocytosis of RPE and prevents accumulation of toxic debris, and thus its mutation may result in RP.[20] In a phase 1 study of six patients with *MERTK* mutation who received subretinal injection of rAAV2-VMD2-hMERTK,[21] three patients showed improved visual acuity, with one of them achieving 20/125 at day 8 (compared with <20/6400 at baseline). The mean FST testing results improved over time (p=0.01) and better in treated eye at day 10 (p=0.02). There was no major change in the central macular or foveal thickness of the treated eyes. This shows the efficacy and safety of *MERTK* gene therapy on the retina.

Congenital stationary night blindness

CSNB is an inherited and non-progressive disease affecting photoreceptors, mainly rods, and bipolar cells. It can be classified based on electroretinogram (ERG) pattern, fundus appearance, and mode of inheritance.[22] CSNB is mainly caused by defects in four genes including *PDE6B*, *CACNA1F*, *NYX*, and *SLC24A1*.[22] Patients often present with poor vision under dim light, delayed adaptation of the dark, and photophobia. Injection of AAV-carrying genes that affect CSNB including iZEG:Cacna1f, AAV2-7m8-*Lrit3*, and AAV2(quadY-F+T-V)-Ple155 has been reported to improve photoreceptor and bipolar cell responses in animal studies (**Table 2**).

iZEG:Cacna1f vector

CSNB with disrupted phototransduction within the bipolar cells is referred to as type 2 CSNB or incomplete CSNB. CSNB2A, the most common form of CSNB, results in poor visual acuity, strabismus, and nystagmus.[23] In a *Cacna1f*-knockout mouse model of CSNB2A that has a loss-of-function mutation of a gene coding for calcium channel CaV1.4,[24] overexpression of *iZEG:Cacna1f* resulted in rescue of visual function, with a well-delineated b-wave on scotopic ERG, which is an indicator of ON-bipolar cells (ON-BC) signaling. This reflects the re-establishment of photoreceptor-bipolar cell synapses.[24] Photopic ERG showed distinct b-wave in all background intensities, compared with no b-wave component in controls. Retinal morphology was preserved in areas with transgenic *Cacna1f* expression. This indicates α1F immune-positive ribbon synapse and preserved cone morphology, which is similar to wild-type photoreceptors. There were also reduced bipolar cells dendritic sprouting and restored mature lamination of cone pedicles. This reveals that high expression of *Cacna1f* may rescue retinal morphology and functions in CSNB2A models.

AAV2-7m8-Lrit3

Leucine-rich repeat immunoglobulin-like transmembrane domain 3 (*LRIT3*) gene is responsible for the protein in the outer plexiform layer of the retina, which affects transmission of signals between photoreceptors and ON-BC.[25] The disrupted signal transmission leads to complete CSNB. In *LRIT3*-knockout mice subjected to right eye intravitreal injection of AAV2-7m8-*Lrit3* (a vector containing *LRIT3* gene),26 LRIT3 proteins were found in rod-to-rod bipolar cells and cone-to-cone bipolar cells synapse. This confirms the effective protein synthesis in the outer plexiform layer. ERG showed a significant b-wave with sustained amplitude under scotopic conditions at 4 months after treatment, compared with no b-wave signals in controls. In addition, transient receptor potential melastatin 1 (TRPM1) was localized at the dendritic tips of the ON-

Table 2. Gene therapies for congenital stationary night blindness

Study	Country	Gene mutated	Groups and sample size	Parameters	Main results
iZEG:Cacna1f					
Waldner et al, 2020[24]	Canada	*Cacna1f*	iZEG:Cacna1f transgenic mice were used by injecting vector DNA into egg of wild type mice.	Immunohistochemical labels, electrophysiological studies, optokinetic response analysis.	Transgenic mice showed a well-delineated b-wave of normal implicit time and subnormal amplitude. Gene transduction rescued α1F immune-positive ribbon synapse, preserved cone morphology, reduced bipolar cells dendritic sprouting, and restored mature lamination of cone pedicles.
AAV2-7m8-*Lrit3*					
Varin et al, 2021[26]	France	*LRIT3*	*LRIT3*$^{-/-}$ mice received intravitreal injections of recombinant AAVs.	Electroretinogram, immunolocalized study, optomotor test.	Mice with gene therapy revealed a partial scotopic b-wave, where b-wave amplitude corresponded to 45% compared to that of *LRIT3*$^{+/+}$ mice. Treated retina showed transient potential receptor melastatin 1 localized at the dendritic tips of rod bipolar cells instead of cell bodies. Optomotor reflexes improved in treated mice under scotopic conditions.
AAV2(quadY-F+T-V)-Ple155					
Scalabrino et al, 2015[28]	United States	*Nyx*	*Nyx*^{nob} mouse model of CSNB1 received subretinal injections of AAV vector plasmid containing Ple155-GFP and Ple155-YFP_NYX.	Electroretinogram, immunohistochemistry, quantitative polymerase chain reaction.	Injected eye of the mice showed improved ERG b-wave. TRPM1 localization was restored to the dendritic tips of bipolar cells and TRPM1 channel gating was completely rescued. AAV-mediated Nyx transcript was found in treated eye.

BC instead of cell bodies. This indicates the restoration of ON-BC signaling cascade. A higher proportion of retinal ganglion cells was found to display ON-responses in treated eyes, indicating a functional rescue. Optomotor responses were improved in treated mice. This reflects that visual perception is rescued together with the transmission defect between photoreceptors and ON-BC.

AAV2(quadY-F+T-V)-Ple155

Apart from *LRIT3* gene, nyctalopin (*Nyx*) is another leucine-rich repeat protein that contributes to complete CSNB. NYX is necessary for the correct localization of TRPM1, for the signaling pathway in ON-BC and light-evoked depolarization.[27] In a study of Nyx-knockout mice that received trans-corneal subretinal or intravitreal injection of AAV vector plasmid containing Ple155-GFP and Ple-YFP_NYX,[28] intravitreal injection of AAV2(quadY-F+T-V)-Ple155 resulted in a strong expression of *Nyx* on the dendritic tips, soma, and axonal terminals of ON-BC. However, subretinal delivery resulted in inefficient transduction in both wild-type or transgenic retina. Subretinal delivery may only promote transduction in the area of surgically induced bleb, whereas intravitreal delivery can induce panretinal expression. Moreover, *Nyx* gene replacement partially rescued b-wave on ERG. The pattern was similar in wild-type mice, with a waveform deflection. Similar to the *Lrit3* gene therapy, *Nyx* gene replacement resulted in co-expression of NYX and TRPM1 in the retina, where TRPM1 was found in both cell bodies and the dendritic tips of the ON-BC. This demonstrates that gene therapy promotes the correct localization of TRPM1 and thus improves signaling pathway of the bipolar cells. Appropriately sized amplicons of *Nyx* transcript were produced in treated retina at days 2 and 30. This demonstrates the potential of *Nyx* gene replacement therapy in human complete CSNB.

Cone-dominated disease

Achromatopsia

Achromatopsia is an autosomal recessive disease that mainly affects the cone photoreceptors, with a lack of all three types of cones. Patients usually present with day blindness, poor visual acuity, photophobia, nystagmus, and poor discrimination of chromatic contrast. Mutation of *CNGA3*, *CNGB3*, *GNAT2*, *PDE6H*, *PDE6C*, and *ATF6* is responsible for >90% of achromatopsia cases.[29] Injection of AAV-carrying genes that affect achromatopsia including AAV8.CNGA3, AAV-hCNGB3, AAV2.GL, and AAV2.NN has been reported to ameliorate cone cell responses in animal and human studies (**Table 3**).

Table 3. Gene therapies for achromatopsia

Study	Country	Gene mutated	Groups and sample size	Parameters	Main results
AAV8. CNGA3					
Ofri et al, 2018[30]	Israel	*CNGA3*	9 day-blind sheep treated with subretinal injection of AAV5 vector carrying transgene for 6 years.	Periodic photopic maze testing, electroretinogram, immunohistochemistry.	Mean maze navigation time and number of collisions with obstacles significantly dropped after treatment. ERG showed improvement in cone function. Staining showed expression of CNGA3 protein colocalized with red/ green opsin in eye with AAV-injected.
Fischer et al, 2020[31]	Germany	*CNGA3*	9 *CNGA3*-linked achromatopsia patients had unilateral subretinal injection of AAV8.CNGA3 with escalating doses, followed up for one year.	BCVA, contrast sensitivity, full-field stimulation threshold, flicker fusion frequency.	Improved mean BCVA of 2.9 letters and mean log contrast sensitivity of 0.33 log were shown comparing to the baseline. Contrast sensitivity testing improved to 0.328 and critical fusion frequency increased by 5 Hz.
Reichel et al, 2021[32]	Germany	*CNGA3*	9 *CNGA3*-mutated patients had subretinal injection of AAV8. CNGA3 in 3 escalating doses, followed up for 1 year.	BCVA, contrast sensitivity, Roth 28-hue color test.	BCVA of the treated eye at year 3 showed an improvement of 4.6 letters with contrast sensitivity improved by 0.23 log. However, color test showed no improvement after year 2.
AAV2. GL and AAV2. NN					
Pavlou et al, 2021[33]	Germany	*CNGA3*	*Cnga3*$^{-/-}$ mice, dogs and non-human primates with subretinal and intravitreal injection of AAV2.GL or AAV2. NN.	Electroretinogram, immunohistochemistry.	Mice with intravitreal injection showed restoration of cone-mediated light responses, and cone-mediated flicker and single-flash responses. Sections proximally and distally to injection site showed positive Cnga3 staining showing the widespread transduction of vector over the retina.
AAV-hCNGB3					
Ye et al, 2016[34]	United States	*CNGB3*	*CNGB3* knockout mice and non-human primates had subretinal injection of AAV-GFP vector containing PR1.7 promotor.	Electroretinogram, quantitative polymerase chain reaction, immunohistochemistry.	Cone-deficient mice showed rescued cone ERG b-wave responses after vector administration for 3 months. Promotors resulted in strong green fluorescence protein expression in photoreceptors especially cones.

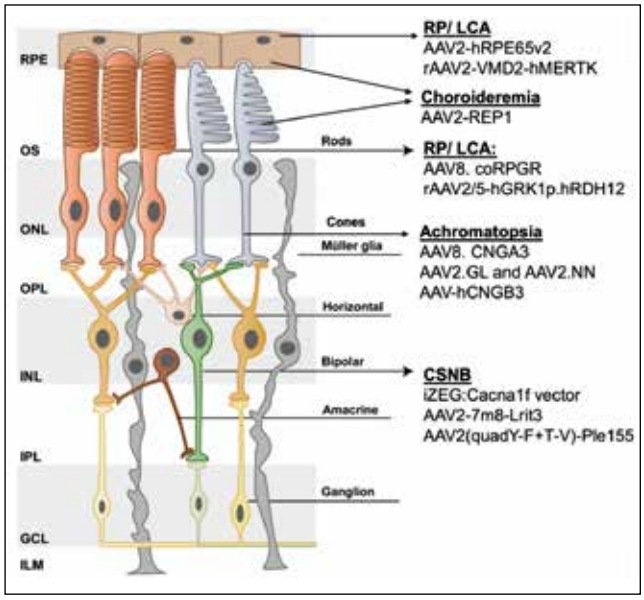

Figure. Schematic diagram showing the targets of various gene therapies. Copyright 2019. MDPI. Copyright under the terms of the Creative Commons CC-BY license.
Abbreviations: RPE retinal pigment epithelium, OS outer segment, ONL outer nuclear layer, OPL outer plexiform layer, INL inner nuclear layer, IPL inner plexiform layer, GCL ganglion cell layer, ILM inner limiting membrane, RP retinitis pigmentosa, LCA Leber congenital amaurosis, and CSNB congenital stationary night blindness.

AAV8. CNGA3

Preclinical studies of day-blind sheep demonstrated the efficacy of cyclic nucleotide-gated channel alpha subunit (*CNGA3*) gene replacement. Nine sheep with *CNGA3* mutation received unilateral subretinal injection of AAV5 vector containing *CNGA3* transgene for 6 years.[30] There was a significant reduction in the mean maze navigation time (p=0.001) and the mean number of collisions with obstacles (p<0.001). This shows an improved visual behavior. The mean navigation time was significantly longer when the treated eye was patched than when the untreated eye was patched (p<0.05). ERG resulted in a significant improvement in cone functions, with a higher critical flicker fusion frequency at 30 and 40 Hz at all four light intensities (p<0.0001). This supports the usage of gene therapy for robust rescue of cone functions in the long term.

In a non-randomized controlled trial of nine patients with *CNGA3*-linked achromatopsia who received a single unilateral subretinal injection of AAV8. CNGA3 (a vector to transduce photoreceptors) in three different doses,[31] at 1 year the mean best-corrected visual acuity (BCVA) improved up to 2.9 letters (p=0.006) and the mean log contrast sensitivity was 0.33 log (p=0.003). There was also improved color vision, with a reduction of chromatic discrimination threshold by 5.3/1000th^2 L*u*v (p=0.04). Four patients had an increased critical fusion frequency by ≥5 Hz. This reflects a new gain of cone function of the retina. Subjectively, validated visual functional questionnaire demonstrated improvements in six of 25 items in terms of the ability to identify letters and numbers, and color vision.

In nine patients with *CNGA3*-mutated achromatopsia who received three doses of subretinal injection of AAV8. CNGA3 in the worse eye,[32] at 3 years BCVA of the treated eye improved by 4.6 letters (p=0.001), with a mean improvement of 0.23 log in contrast sensitivity (p=0.019). The color contrast sensitivity improved in the first 2 years but not beyond. Microperimetry did not show significant improvement over time. However, A3-PRO, a questionnaire to assess the quality of life, revealed that patients had improved ability in fixating, recognizing letters or numbers, and photoaversion.

AAV2.GL and AAV2.NN

In a model of achromatopsia using *CNGA3*-knockout mice that received intravitreal injection of AAV2.GL and AAV2.NN (both vectors achieved widespread panretinal transduction in the mice, dogs, and non-human primates. Both could transduce human photoreceptors using human retina *ex vivo* culture),[33] photopic ERG showed restored single-flash responses and cone-mediated flicker. B-wave amplitude was higher for 1, 3, and 10 cf.s/m^2 (p<0.001 for all). Cnga3 was stained proximally and distally to the site of vector injection and cones. This shows that gene therapy effectively promotes *CNGA3* distribution and localization.

AAV-hCNGB3

50% cases of achromatopsia were due to the mutation of the cyclic nucleotide gated channel beta subunit (*CNGB3*) gene. In *CNGB3* deficient mice subjected to subretinal injection of AAV-hCNGB3 vectors containing a 1.7-kb L-opsin promotor (PR1.7),[34] vectors containing PR1.7 promotors showed a high expression of green fluorescence protein, a marker for cone cells, in short, medium, and long cone types, compared with those without promotors. mRNA level of green florescence protein increased with the induction of vector with PR1.7 promotor. This reflects the role of PR1.7 promotor in upregulating cones survival upon gene therapy. After 3 months of injection, transgenic mice revealed a significant improvement in photopic b-wave amplitude in ERG (p=0.028). This suggests that the AAV-hCNGB3 may be a treatment option in patients with *CNGB3*-induced achromatopsia.

Generalized retinal dystrophies

Leber congenital amaurosis

LCA is a heterogeneous and progressive rod-cone dystrophy caused by mutation of 13 genes. It is a less common and more severe RP subtype, with genetic overlap with RP, but presents with earlier onset and faster progression.[15] LCA type 2 mainly involves *RPE65* mutation, a gene that encodes for 11-*cis*-retinol required for RPE activity. Patients often present with weakly reactive pupils, poor visual acuity, nystagmus, and eventually vision loss.

Table 4. Gene therapies for Leber congenital amaurosis

Study	Country	Gene mutated	Groups and sample size	Parameters	Main results
AAV2-hRPE65v2					
Maguire et al, 2009[35]	Italy	*RPE65*	12 patients with *RPE65*-associated LCA were given single subretinal injection of AAV2-hRPE65v2 for up to 2 years.	BCVA, dark adaptometry, pupillometry, ERG.	7 patients showed substantial and stable improvement in visual acuity, with all patients having improvement in visual field and pupillary responses. A large interocular difference in full-field sensitivity was found in 5 patients.
Ripamonti et al, 2015[36]	United Kingdom	*RPE65*	8 subjects with *RPE65* mutation received rAAV vector expressing human *RPE65*.	Dark-adapted spectral sensitivities, cone plateau spectral sensitivities.	Improved rod function was found in 2 patients and improved rod sensitivity in 1 patient. Cone sensitivity was found to be improved in 1 patient.
rAAV2/5-hGRK1p.hRDH12					
Feathers et al, 2019[38]	United States	*RDH12*	*Rdh12*$^{-/-}$ mice received unilateral subretinal rAAV2/5-hGRK1p.hRDH12 vector.	Immunostaining, immunoblotting, electroretinogram.	Treated eyes showed stable expression of RDH12 in photoreceptor inner segments. Retinal reductase activity was restored after vector injection. No significant difference in ERG magnitude was found between non-injected and injected eyes. RDH12 expression was found to protect against light damage.

Injection of AAV-carrying genes that affect LCA including AAV2-hRPE65v2 or rAAV2/5-hGRK1p.hRDH12 has been reported to enhance photoreceptor responses in human and animal studies (**Table 4**).

AAV2-hRPE65v2

A lack of *RPE65* leads to insufficient 11-*cis*-retinol and inability of rods to respond to light. In a phase 1 trial of 12 patients with *RPE65*-associated LCA who received subretinal AAV2-hRPE65v2 in the worse-seeing eye and were followed up for 2 years,[35] all patients had better vision in a dim environment at 2 weeks (with children having higher BCVA at baseline). All patients had improvement in visual field. Younger patients had improvement in full-field sensitivity to white light, with a gain of several log units of sensitivity. An 8-year-old patient even had a light sensitivity similar to age-matched normal-sighted controls. Pupillometry showed ≥2 log unit increase in pupillary light response. Full-field ERG photopic responses occurred in a part of the injected retina on day 30 and then in several other parts on day 60 and day 90. This indicates the clinical benefit of subretinal gene therapy in preventing retinal degeneration.

In a phase 2 trial of eight young adults and children with *RPE65* mutation who received subretinal injection of rAAV2/2. hRPE65p.hRPE65,[36] two patients showed improvement in rod functions in dark-adapted spectral sensitivities at year 3. Both showed substantial improvement in sensitivity at month 2 or 4, which remained constant until month 12 at all wavelengths. The spectral sensitivity showed a M-cone shape during the cone plateau; there was a switch from rod-mediated vision to cone-mediated after bleaching. Nevertheless, dark-adapted sensitivity in the remaining six patients remained cone-like, without much improvement or declination.

rAAV2/5-hGRK1p.hRDH12

Retinal dehydrogenase 12 (RDH12) is an enzyme that reduces 11-*cis* retinaldehyde and all-trans retinaldehyde for the visual cycle and detoxification of lipid peroxidation.[37] Its mutation has been linked to LCA and autosomal dominant RP. In an *in vivo* study of *Rdh12*-knockout mice with subretinal injection of different doses of rAAV2/5-hGRK1p.hRDH12 (an AAV vector containing *RDH12* cDNA),[38] there was an increased average initial rate of all-*trans* retinol formation of 0.046 pmol min^{-1} μg protein^{-1} in treated mice, compared with 0.013 pmol min^{-1} μg protein-1 ($p<0.01$) in controls. This reflects the ability of gene therapy to restore retinal reductase activity. Moreover, *Rdh12*-knockout mice were bred onto albino mice to produce Rpe65-Leu450 knockout species. ERG under scotopic condition revealed improvement in rod b-wave, rod-cone a-wave, and rod-cone b-wave ($p<0.001$) in treated eye of *Rdh12*-knockout mice after 1 week, compared with controls. This reflects that *RDH12* gene therapy may protect patients with LCA against light damage.

Choroideremia

Choroideremia is an X-linked recessive disorder that leads to loss of night vision and gradually peripheral vision loss. It is commonly caused by the mutation of *CHM*, a gene that encodes ras-associated binding escort protein 1 (REP1). Subsequently, degeneration of photoreceptors and RPE, neuronal cell death, and retinal remodeling occur.[39] Injection of AAV-carrying genes that affect choroideremia including AAV2-REP1 has been reported to achieve variable results in terms of visual acuity and retinal sensitivity in clinical trials (**Table 5**).

AAV2-REP1

In a phase 1 trial of six patients with choroideremia who received subfoveal injection of rAAV2.REP1 (a recombinant

Table 5. Gene therapies for choroideremia

Study	Country	Gene mutated	Groups and sample size	Parameters	Main results
AAV2. REP1					
Dimopoulos et al, 2018[40]	Canada	*CHM*	6 patients confirmed with choroideremia received single subfoveal injection of rAAV2. REP1 and were followed up for 2 years.	BCVA, microperimetry, fundus autofluorescence.	5 patients did not experience significant visual acuity gain over 2 years. Microperimetry sensitivity or area of preserved RPE did not reveal changes after vector administration compared to untreated eyes.
Fischer et al, 2019[41]	Germany	*CHM*	6 patients with diagnosed choroideremia received single AAV2-REP1 subretinal injection and were followed up for 24 months.	BCVA, microperimetry, fundus autofluorescence.	Treated eyes gained a mean of 4.7 and 3.7 letters at months 3 and 24 respectively, with a mean difference of 3.7 letters compared to the fellow eye. Retinal sensitivity in the treated eyes showed an increase of 10.3. 5 patients had improvement in peak retinal sensitivity and/ or gaze fixation area.
Lam et al, 2019[42]	United States	*CHM*	6 patients with choroideremia received subfoveal injection of AAV2-REP1 in the worse-sighted eye and were followed up for 24 months.	BCVA, microperimetry, contrast sensitivity, color vision.	BCVA changes in letter scores ranged from -1 to +10 letters from baseline in the treated eye while that ranged from -2 to +4 letters in untreated eyes. No microperimetric changes, contrast sensitivity and color vision were detected at month 24 compared to baseline.
Fischer et al, 2020[43]	Germany	*CHM*	6 patients with chorioderemia had subretinal injection of AAV2-REP1 followed up for 12 months.	BCVA, microperimetry, fundus autofluorescence.	5 patients had improved BCVA yet 1 patient lost 14 letters at month 12. 5 patients had improved mean retinal sensitivity of 2.3 dB and peak retinal sensitivity of 2.8 dB. Gaze fixation area was improved to -36.1 deg^2.
MacLaren et al, 2014[44]	United Kingdom	*CHM*	6 patients with choroideremia were administrated with subfoveal AAV.REP1 and followed up for 6 months.	BCVA, microperimetry, retinal sensitivity tests.	There was a mean gain of VA by 3.8 letters in treated eyes. Maximal sensitivity increased from 23.0 to 25.3 dB after gene therapy. Increased retinal sensitivity by 1.7 was found over 6 months.
Xue et al, 2018[45]	United Kingdom	*CHM*	14 patients with CHM gene mutation had unilateral subretinal injection of AAV2. REP1 vector and followed up for 2 years.	BCVA, microperimetry, fundus autofluorescence	Mean visual acuity improved by 4.5 letters while untreated eyes declined by -1.5 letters. However, there was a slight decline of mean retinal sensitivity of treated eyes from 4.0 to 3.3 dB at 2 years. Area of retinal autofluorescence was similar between groups.

vector with REP1 expression and prenylation activity against ras-associated binding substrate),[40] at 2 years five patients did not have significant BCVA gain and only one patient had an improvement of >15 letters. Treated eyes demonstrated linear decline of area of fundus autofluorescence (correlating to area of surviving photoreceptors) with time ranging from -0.012 to -0.046 mm^2/month. The rate of decline in treated and untreated eyes was similar (p=0.062). Spectral domain optical coherence tomography in four patients showed a more prominent central foveal thickness loss in the treated eye than in the untreated eye. Microperimetry showed no improvement in mean sensitivity in the treated eyes.

In a phase 2 study of six patients with choroideremia who received AAV2-REP1 therapy,[41] at year 2 the mean BCVA was 20/50 in the treated eyes and 20/40 in the untreated eyes; the difference was 3.7 letters and not significant (p=0.43). Retinal sensitivity was similar in treated and untreated eyes (p=0.74), although five of six treated eyes showed improvement in mean retinal sensitivity and peak retinal sensitivity.

In a phase 2 trial of six patients with choroideremia who received subretinal injection of AAV2-REP1,[42] subjective visual observation in the treated eye suggested mainly vision 'clearer' or 'shaper', followed by 'mild shade'. At year 2, the change in letter scores varied from -1 to +10 letters in the treated eye and from -2 to +4 letters in the untreated eye. In two patients, BCVA in the treated eye showed improvement of 5 and 10 letters. However, there was no change in visual field, contrast sensitivity and color vision, and area of foveal autofluorescence. Similarly, in a phase 2 trial of six patients with choroideremia who received subretinal AAV2-REP1,[43] at year 1 four patients experienced minimal BCVA changes ranging from -4 to +1 letters, with one patient gaining 17 letters. Microperimetry in the treated eye showed increased mean retinal sensitivity of 2.3 dB, peak retinal sensitivity of 2.8 dB, and gaze fixation area of -36.1 deg^2. The fundus autofluorescence area showed a mean annual decline of 16%, whereas the ellipsoid zone showed a decrease of 14% at year 2.

In a phase 1 and 2 trial of six patients treated with subfoveal

injection of AAV.REP1 for choroideremia,[44] there was a mean gain of 3.8 letters in visual acuity at month 6. Two patients with a reduced visual acuity at baseline gained 21 or 11 letters. In the treated eye, dark-adapted microperimetry showed that the point of maximal sensitivity increased by 2.3 dB and the mean retinal sensitivity increased by 2.5 dB. The mean retinal sensitivity increase was correlated with the dose injected per unit area (r=0.82, p=0.04). In a study of 14 patients with choroideremia who had subretinal AAV2.REP1 vector injection,[45] at 2 years there was a median improvement of BCVA of 4.5 letters in treated eyes and a decline of 1.5 letters in untreated eyes (p=0.04). The mean retinal sensitivity declined from 4.0 dB to 3.3 dB at 2 years (p=0.07). However, measurement of fundus autofluorescence area showed no significant difference between treated and untreated eyes.

Among all gene therapies, voretigene neparvovec-rzyl (Luxturna) is the only approved treatment for inherited retinal dystrophies.[46] It targets patients with biallelic *RPE65* mutation–associated retinal dystrophy (including LCA and RP) and those with sufficient viable retinal cells. Voretigene neparvovec-rzyl is injected beneath the retina to allow a new and functional gene copy to pass into the RPE. It is approved for patients aged ≥1 year. Genetic testing on both *RPE65* gene is important in confirming the diagnosis of LCA or RP at an early stage before commencing injection therapy. Subretinal delivery of AAVs requires pars plana vitrectomy, which increases risks of retinal detachment, cataract, endophthalmitis, and even blindness.[47] Voretigene neparvovec-rzyl injection costs US$425 000 per eye and thus imposes huge financial burden on patients.

Application of gene therapy in Chinese patients with inherited RD

There is a lack of clinical trials of gene therapy for retinal diseases in the Chinese population. In China, gene therapeutics for hematological and immunological disorders such as hemophilia, thalassemia, severe combined immune deficiency, and chronic granulomatous disease have been reported.[48] Gene therapy for Chinese patients with RD may be similar to that for Western populations if the genes identified are compatible with those identified in previous trials. The genetic pattern of RD in Chinese eyes is summarized in **Table 6**.

In the Chinese population, most inherited RD is autosomal recessive secondary to *USH2A* mutation, leading to non-syndromic RP. *RHO* and *RGRP* are common genes causing autosomal dominant and X-linked RD, respectively.[49] In Shanghai patients with RP, the commonest gene mutation for rod-dominant diseases was *USH2A* (18%), *CYP4V2* (15%), *RYS* (7%), *RPGR* (4%), *RHO* (4%), and *RP1* (4%).[50] In the Zhongshan population, the most frequently involved gene were *USH2A* (9%), *RHO* (6%), and *RPGR* (4%).[51] Similarly, in Shenyang patients, *USH2A* was the most commonly mutated gene (40%), followed by *RP1* (16%) and *EYS* (9%).[52] This may indicate the use of AAV8.coRPGR in RD patients to improve visual acuity and visual field. *LRIT3* and *NYX* mutations were found in Zhongshan and Guangdong patients with CSNB, respectively.[53,54] This suggests the role of AAV2-7m8-Lrit3 and AAV2(quadY-F+T-V)-Ple155 in restoring ON-BC functions and localizing TRPM1 in Chinese patients. Cone dystrophies in

Table 6. Genes involved in Chinese patients with inherited retinal dystrophies

Study	City	Group and sample size	Genes involved
Wang et al, 2018[49]	Beijing	319 patients with inherited RD.	*RHO* is the commonest disease-causing gene for autosomal dominant RD. *USH2A* is the commonest disease-causing gene for autosomal recessive RD. *RPGR* is the most common X-linked RP causing gene.
Gao et al, 2019[50]	Fudan	1243 patients with clinically suspected RP.	The commonest gene mutation was *USH2A* (18%), *CYP4V2* (15%), *RYS* (7%), *RPGR*, *RHO*, and *RP1* (each 4%).
Xu et al, 2014[51]	Zhongshan	157 patient with RP.	The most frequently harboured mutations were *USH2A* (9%), *RHO* (6%) and *RPGR* (4%).
Sun et al, 2020[52]	Shenyang	87 patients with RP.	Commonest mutation of RP were *USH2A* (40%), *RP1* (16%), *EYS* (9%), *AGBL5* (4%), *RHO* (4%).
Dan et al, 2017[53]	Zhongshan	8 patients with CSNB.	*LRIT3* gene mutation was found but not *CABP4* and *GRP179*.
Xiao et al, 2006[54]	Guangdong	2 families with CSNB1.	*NYX* mutation was discovered, with sequence analysis showing c.281G>C and c.302T>C.
Li et al, 2014[57]	Zhongshan	138 patients with cone dystrophies and 129 patients with LCA.	*CNGA3* mutation was found in 46 patients with cone dystrophies, with 18 patients with achromatopsia and 28 patients with cone-rod dystrophies.
Xu et al, 2020[55]	Beijing	91 patients with LCA and 57 patients with early onset severe retinal dystrophies.	In LCA patients *AIPL1* (11.0%), *RPGRIP1* (8.8%), *CEP290*, *GUCY2D* and *RPE65* (each 7.7%) were involved. In EOSRD patients, *RPGR* (12.3%), *CRB1* (10.5%), *RPE65* (10.5%), *RDH12* (7.0%), *RP2* (5.3) were involved.
Han et al, 2020[56]	Beijing	48 patients with choroideremia.	*CHM* gene mutation was shown, with 11 splicing sequence variants, 8 non-sense sequence variants, and 4 copy number variants.

Zhongshan populations were due to the mutation of *CNGA3*, which suggests the use of AAV8.CNGA3 to improve BCVA and contrast sensitivity in Chinese patients. Regarding generalized retinal dystrophies, LCA mutation was mostly attributed to *AIPL1* (11.0%), followed by *RPGRIP1* (8.8%), *CEP290*, *GUCY2D* (7.7%), and *RPE65* (7.7%).[55] In patients with early-onset severe retinal dystrophy, *RPGR* (12.3%), *CRB1* (10.5%), *RPE65* (10.5), *RDH12* (7.0%), *RP2* (5.3%) were involved. Thus, *RPE65* and *RDH12* gene therapy may be useful in Chinese LCA patients. In Beijing patients with choroideremia secondary to *CHM* mutation, AAV.REP1 vector administration may confer beneficial visual effects.[56]

Conclusion

Gene therapies using AAVs to encode a specific gene that is mutated in RDs are emerging. Clinical and animal studies have shown that gene therapy confers beneficial visual effects in patients with RP, CSNB, achromatopsia, LCA, or choroideremia. In studies involving Western populations, the genes found to be affected are mostly similar to those in the Chinese population. This gives rise to the potential use of gene augmentation in Chinese patients with inherited RD. A thorough understanding of the emerging gene therapy of different RD subtypes may allow more personalized management.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

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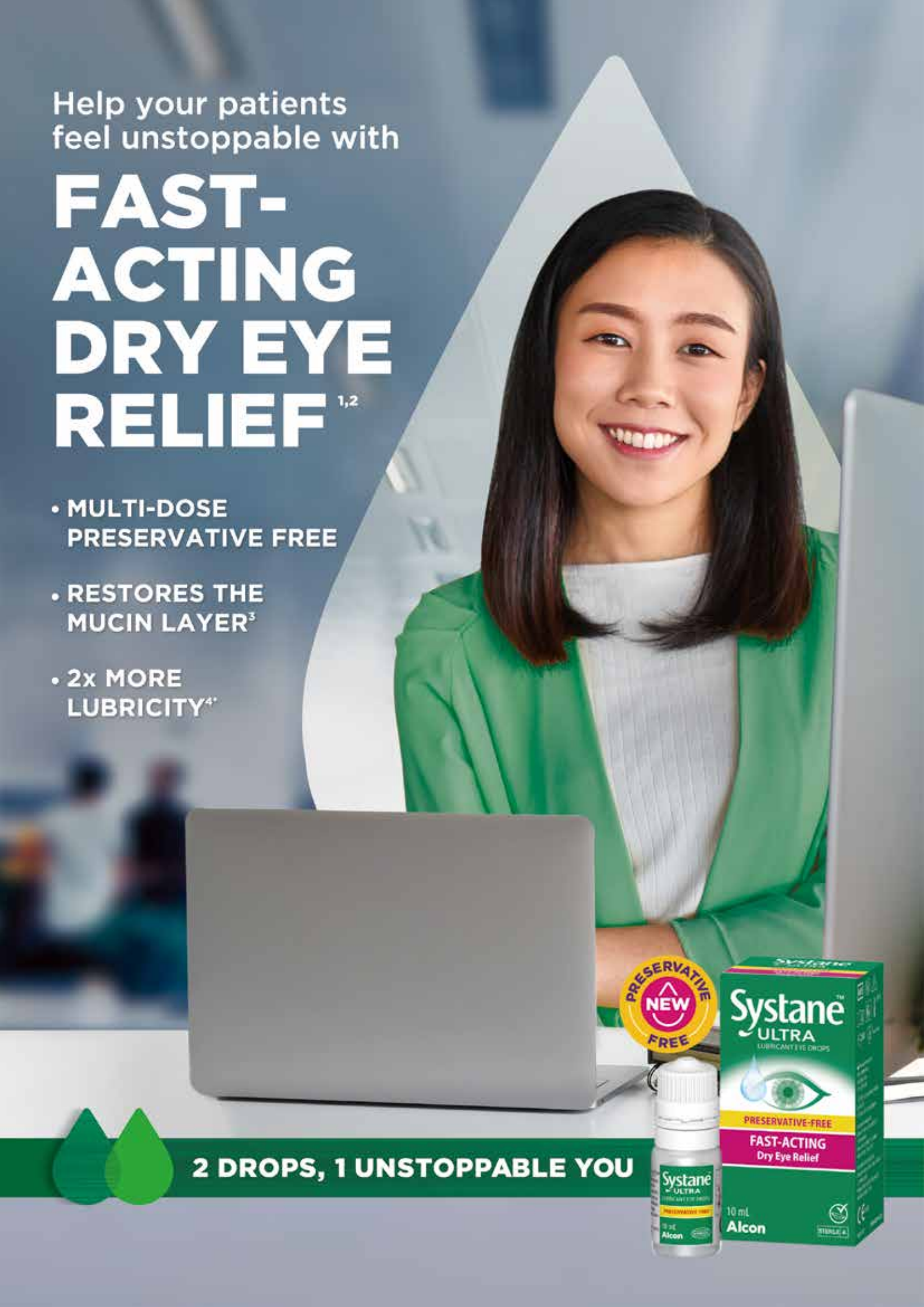

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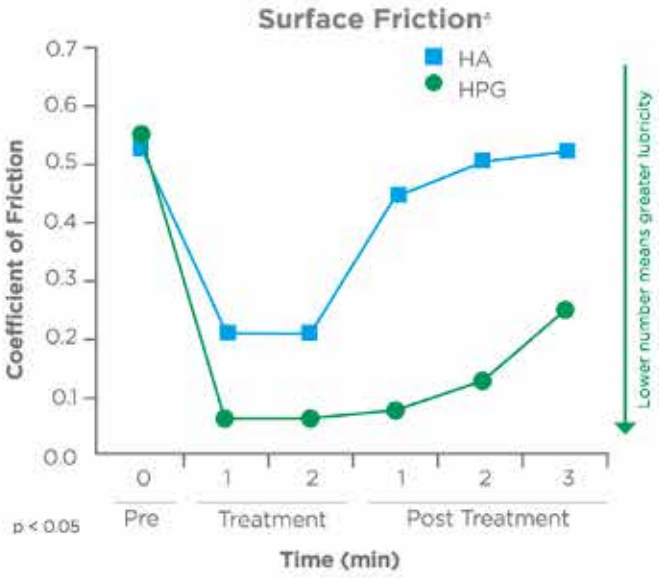

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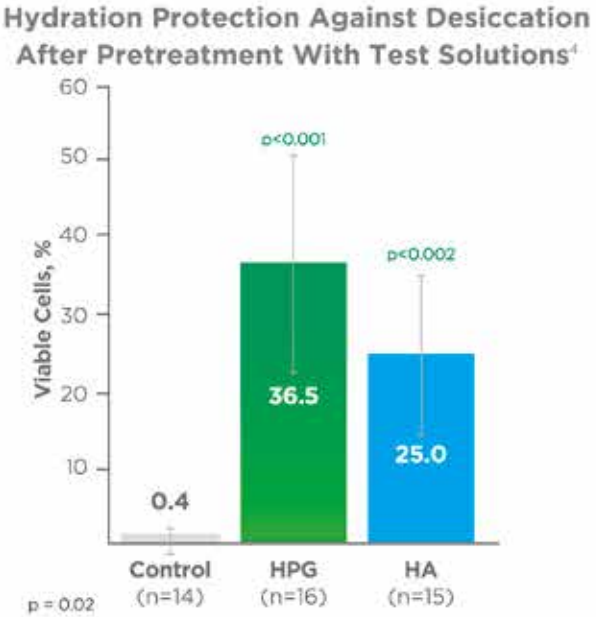

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Intraocular lens power calculation in patients with corneal ablative treatments or corneal pathologies: perspective

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Abstract

Intraocular lens power calculation in patients with abnormal corneas secondary to ablative treatments or pathologies is challenging. The historical data methods, which collect data before corneal ablative treatment, are preferred for the intraocular lens power calculation. It is recommended to perform the calculation with several formulas and to compare the calculated lens powers. The Barrett True-K (total keratometry) provides good prediction after myopic and hyperopic laser treatment. In general, mild myopia should be aimed for, and aspheric lenses are preferred in these cases. The corneal irregularity in patients with keratoconus necessitates measurements of the back surface of the cornea. Postoperative myopia should be aimed for owing to the risk of hyperopic refractive outcomes. Implantation of toric lenses is only recommended in selected cases. In patients with Fuchs' endothelial dystrophy, preoperative measurements should be performed after administration of hyperosmolar eye drops and as late as possible during the course of the day. Measurements should include the posterior corneal surface. Owing to the hyperopic shift after Descemet membrane endothelial keratoplasty or Descemet stripping automated endothelial keratoplasty, a slight myopia should be aimed for, followed by cataract surgery in future. In exceptional cases, the implantation of toric lenses may be considered.

Key words: Corneal surgery, laser; Fuchs' endothelial dystrophy; Keratectomy; Keratoconus

Calculation after photorefractive keratectomy or laser in situ keratomileusis

The calculation of intraocular lens (IOL) power in patients after laser vision correction (LVC) treatment is challenging, particularly increasingly more pretreated patients reach the age when cataract surgery is necessary. During the course of LVC, changes in the cornea occur, which must be taken into account in the IOL calculation.

Three factors may result in refractive errors.[1] First, the corneal refractive power (K-value) is not measured directly. Instead, the radius of corneal curvature is determined, and the refractive power is derived from it using the corneal refractive index. Owing to the changed ratio of anterior to posterior corneal surface caused by LVC, the assumed corneal refractive index is not valid and the calculated K-values are incorrect. After a myopic LVC, too high values are determined. Consequently, an IOL with too little power is implanted, and patients become more hyperopic than intended. The opposite is true for a hyperopic LVC. To solve this issue, the anterior and posterior surfaces should be measured using the Scheimpflug camera or optical coherence tomography (OCT).

Second, the radius of the corneal curvature is measured by devices outside the optical center, and the central curvature is estimated. Therefore, after a myopic LVC, the cornea is considered steeper than it actually is in the center when measured peripherally (**Figure**).

Third, the K-value is used in third-generation formulas (ie, Hoffer Q, Holladay 1, and SRK/T) to calculate the effective lens position and the lens power. Based on incorrect K-values, myopic LVC underestimates the effective lens position and the lens power to be implanted. Thus, the Aramberri double K method uses the preoperative K-value to calculate the effective lens position and the postoperative K-value to calculate the lens power.

There is no consensus on the superiority of any formula for IOL calculation after LVC. Some are difficult to implement in practice, as they require manual calculations of lens power or special measuring devices. The most common options in clinical practice with good results are presented below.

The historical data methods, which collect data before LVC, are preferred to the non-historical data methods. If post-LVC refraction is used for calculations, values should be determined approximately 6 months after surgery to prevent bias from subsequent myopic cataract. Non-historical data methods can be divided into regression formulas and formulas based on measurement of the anterior and posterior corneal surfaces using the Scheimpflug camera or OCT. In the absence of data regarding LVC, corneal topography is recommended prior to IOL implantation to assess the nature of LVC and any corneal irregularities.

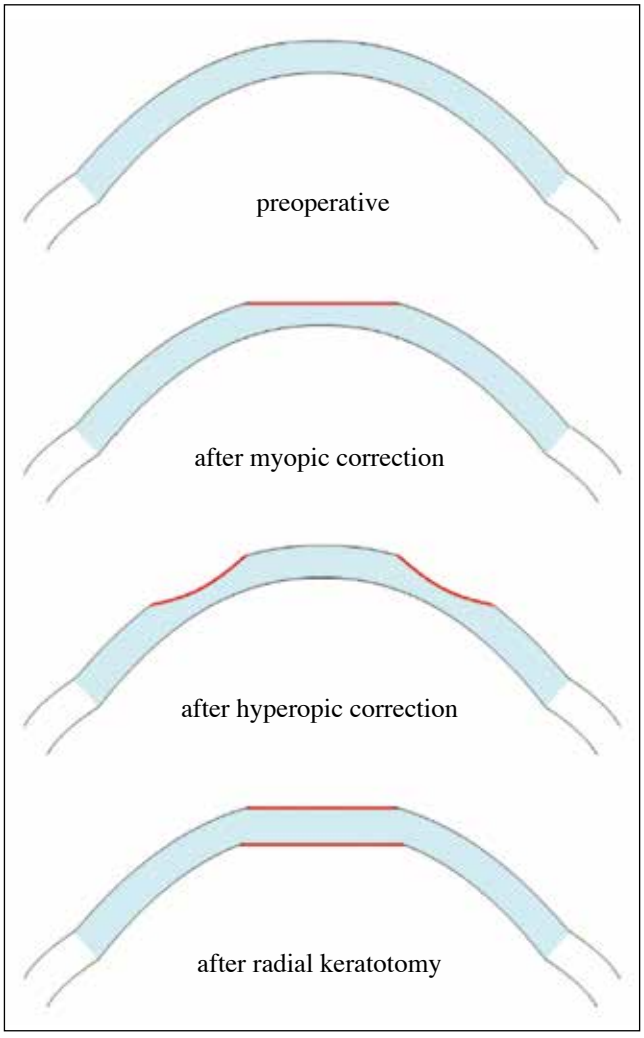

Figure. Corneal changes after ablative treatments

The American Society of Cataract and Refractive Surgery (ASCRS) website (iolcalc.ascrs.org) and the Asia-Pacific Association of Cataract and Refractive Surgeons (APACRS) website (apacrs.org) provide formulas and calculations and include an option for toric lenses.

Non-historical data methods for IOL calculation after myopic and hyperopic refractive surgery include (1) Holladay 2: IOLMaster 500 & 700, Lenstar LS 900, Holladay IOL Consultant Software & Surgical Outcomes Assessment (HICSOAP); (2) Shammas-PL (after myopic LVC) or Shammas-PHL (after hyperopic LVC): ASCRS, Lenstar LS 900; (3) Haigis-L: ASCRS, IOLMaster 500 & 700; (4) OCT-based formula: ASCRS; and (5) Barrett True-K no-history: ASCRS, APACRS, IOLMaster 700, Lenstar LS 900.

Historical data methods for IOL calculation after myopic and hyperopic refractive surgery include (1) variations of double-K Holladay 1: ASCRS, HICSOAP, Pentacam; (2) Masket and modified-Masket: ASCRS, Lenstar LS 900; and (3) Barrett True-K: ASCRS, APACRS, IOLMaster 700, Lenstar LS 900, Pentacam.

Masket is a modification of SRK/T in formerly myopic eyes or Hoffer Q in formerly hyperopic eyes. The change in refraction secondary to LVC must be known. It provides more accurate results than the Haigis-L in post-myopic eyes.[1] The pre-LVC refraction is also required for the Barrett True-K. Compared with other formulas in the ASCRS calculator, Masket achieves comparable or better predictions after myopic correction, as does the Barrett True-K no-history.[2]

In case there are no historical data, obtaining keratometry measurements from the Pentacam, the total corneal refractive power or the true refractive power in the 4-mm zone are good options for IOL power calculations using the Haigis formula.[3] An alternative is the Shammas no-history formula in combination with the true net power in the 4-mm zone.[4]

Precise measurements of the cornea can be made using ray-tracing. Calculations are offered directly on the GALILEI and SIRIUS or in the OKULIX and PhacoOptics programs. Calculations based on intraoperative aberrometry with the Optiwave Refractive Analysis show good results, compared with the Haigis-L or Masket, as does the OCT formula from the ASCRS website.[5]

Calculating multifocal lenses is even more challenging. For post-myopic eyes, the Barrett True-K no-history is the best non-historical data method of the ASCRS calculator. If pre-LVC data are available, the Masket, modified-Masket, Barrett True-K, and Haigis-L are comparable and superior to the Shammas-PL.[6] After hyperopic LVC, all available ASCRS formulas are suitable for calculation, except for the modified-Masket.[7]

The IOLMaster 700 allows measurement of the posterior corneal surface using swept source OCT and thus the total keratometry. The difference between standard keratometry and total keratometry values after LVC is 0.21-0.36 diopters.[8] Calculations using the standard Haigis + total keratometry are comparable to those using the Haigis-L + standard keratometry and Barrett True-K no-history + standard keratometry.[9] The use of total keratometry (rather than standard keratometry) improves the performance of the Barrett True-K.[8] In the IOLMaster, total keratometry is then selected in the calculation, and the patient is not indicated as preoperative. In the APACRS version of the Barrett True-K, the refractive power of the corneal posterior surface and thickness can be entered separately. These calculations give better results after myopic LVC than those with the standard Haigis + total keratometry, Haigis-L + standard keratometry, and Shammas-PL + standard keratometry. If no pre-LVC data are available, the APACRS version of the Barrett True-K currently provides the best prediction for post-myopic and hyperopic patients.[8]

The ASCRS website allows calculations using different formulas with one-time data entry. The suggested lens powers can be compared and outliers can be detected. The mean of the remaining values can be used for IOL selection.

No single method is superior to others. Calculations should be made with several formulas, and the calculated lens powers compared. Nonetheless, the Barrett True-K formula provides good predictions after myopic and hyperopic LVC. It can be used with or without pre-LVC data. To avoid undesirable hyperopic results, a mild myopia (a spherical equivalent of -0.25 to -0.50 diopters) should be aimed for. As positive spherical aberrations occur after myopic LVC, aspheric lenses with negative aberrations should be implanted in these cases.

Calculation after to small incision lenticule extraction (SMILE)

SMILE is a relatively new method for correction of ametropia, and its data are limited. Nonetheless, both LASIK and SMILE are excision procedures with removal of corneal tissue and thus similar limitations and errors in IOL power calculation are assumed. Principles that apply to LASIK may also be valid for SMILE. The use of the Barrett True-K no-history, Barrett True-K, or Masket can lead to good results.[10]

Calculation after radial keratotomy

With radial keratotomy, in contrast to the ablative methods, the anterior and posterior corneal surfaces are flattened (**Figure**). Postoperatively, the corneal refractive power is overestimated when normal measurement methods are used. In addition, the cornea is unstable after radial keratotomy, and the instability is exacerbated by the incisions made during cataract surgery, further decreasing the predictability of the IOL calculation. The preinstalled formulas of the Lenstar LS 900 and the Haigis-L of the IOLMaster 700 can be used for the calculation, according to the manufacturer. The ASCRS and APACRS websites also offer options. The Barrett True-K yields the best results. If no pre-LVC refraction is available, the Haigis-L, OCT-based formula, and Barrett True-K no-history are suitable.[11,12]

IOL calculation in patients with keratectasia

Keratectasia usually occurs primarily in patients with keratoconus. During the course of keratoconus, myopia and astigmatism occur. Refractive errors after cataract surgery are common, because the cornea is usually irregular, and keratometry does not provide reliable values. In addition, measurement of K-values and axial lengths (AL) often do not correspond to those of the optical axis, because the apex (the steepest part of the cornea) is usually located in the inferior region. The reliability of the corneal measurement decreases with increasing keratoconus. A stable keratoconus is necessary for reliable IOL calculation. The Pentacam tends to measure lower K-values than optical biometry devices such as IOLMaster or Lenstar LS 900.[13] Devices that measure anterior and posterior corneal surfaces to determine total refractive power (such as the Pentacam) should be used. IOL power calculation using total corneal refractive power of the central 3 mm zone instead of simulated K-values leads to a myopic shift. Simulated K-values based on anterior surface measurements overestimate corneal refractive power and may result in hyperopic results. For severe keratoconus, a standard K-value of 43.25 diopters (rather than actual K-values) can be used for calculation. In general, a myopic outcome should be aimed for.

Wearing contact lenses flattens the anterior cornea and alters the astigmatism magnitude and axis. Recovery rates of corneal warpage range from about 2 weeks for soft contact lenses to 9 weeks for rigid gas-permeable lenses. Many patients with keratoconus are impaired during daily routine without rigid contact lenses. Hence, maintaining a contact lens-free period prior to measurements for keratorefractive surgery is difficult. To obtain reliable K-values, serial measurements are recommended until the values are stable.[14]

The HICSOAP software offers a Holladay II version specifically for keratoconus, but it is inferior to the standard Holladay II. The Kane version modified for keratoconus (Kane-keratoconus) includes toric IOL calculations (iolformula.com). The Kane-keratoconus performs better than Hoffer Q, SRK/T, Holladay I and II, Haigis, Barrett

Universal II, and standard Kane at all stages of keratoconus. Alternatively, good results can be achieved using the Barrett Universal formula. The SRK/T is a good option for long eyes, as it leads to a myopic shift at high K-values and axial lengths, which can compensate to some extent for the rather hyperopic outcome of patients with keratoconus.[15] For SRK/T, adjustments to the target refraction are recommended to correct for errors in effective lens position prediction as follows: 0.75 to 1.5 diopters in stage II and 2.0 to 3.0 diopters in stage III.[16]

Regarding lens design, toric lenses are a good option for correcting regular astigmatism. Nonetheless, in patients with keratoconus, the astigmatism is often irregular, which creates difficulties in both IOL calculation and IOL positioning. Higher-order aberrations can be exacerbated. In cases that keratoplasty is required in future or that form-stable contact lenses are worn postoperatively, toric IOL are not recommended. The pinhole lens IC-8 is suitable to reduce higher-order aberrations and improve central vision.

Patients with keratoconus have much higher K-values than healthy individuals. If the need for penetrating keratoplasty or deep anterior lamellar keratoplasty is foreseeable, it may be appropriate to anticipate the postoperative keratometric value and to calculate the IOL power accordingly. Otherwise, using the high preoperative K-values for IOL calculation results in a lower power to be implanted and considerably high hyperopic shifts after penetrating keratoplasty or deep anterior lamellar keratoplasty.

IOL calculation in patients with Fuchs endothelial dystrophy

Phacoemulsification with lens implantation can be performed separately before or after Descemet membrane endothelial keratoplasty (DMEK) or Descemet stripping automated endothelial keratoplasty (DSAEK) in Fuchs endothelial dystrophy or even combined as triple-DMEK or triple-DSAEK. For IOL calculation, the corneal posterior surface should be included in the preoperative measurements, as the ratio of anterior to posterior surface is altered, compared to healthy eyes. It should be noted that a myopic shift occurs in calculations with the total corneal refractive power instead of the simulated K-values.

In Fuchs endothelial dystrophy, the corneal edema leads to a myopic change secondary to the flattening of its posterior surface. In addition, the refractive indices change secondary to the disturbed arrangement of the fibrils. Therefore, measurement of non-preoperated eyes is more difficult. To reduce distortions, measurements should be made as late as possible after applying hyperosmolar eye drops. In case of a pronounced cornea guttata, a triple-procedure is not recommended, because central guttae lead to unreliable values.

Although the refractive power of the anterior corneal surface decreases only slightly, the absolute value of the refractive power of the posterior surface increases and thus total corneal refractive power decreases. A hyperopic shift occurs after DMEK or DSAEK. This is more pronounced in thicker (more edematous and decompensated) cornea. The greater the ratio of the radius of the posterior surface to that of the anterior surface, and the greater the posterior asphericity quotient (Q-value) [ie, the flatter the posterior surface], the higher the hyperopic shift. Considering only corneal thickness or posterior corneal radius is not sufficient to estimate the risk of hyperopic shift.[17] Owing to the hyperopic shift after DMEK, a myopic outcome of -0.5 to -1.0 diopters should be aimed for. The shift after DSAEK is slightly higher than that after DMEK. A target refraction of -1.5 diopters should be aimed for in order to prevent postoperative hyperopia after triple-DSAEK.[18] The higher the preoperative posterior Q-value, the higher the risk of a hyperopic shift and the stronger the myopic target refraction should be aimed for. The myopic target refraction should be set somewhat lower if decongestant eye drops are applied before measurement.

Compared with Hoffer Q, Holladay I, and Haigis, the SRK/T and the use of K-values of the IOLMaster without including the posterior corneal surface show the lowest deviations from ray-tracing-based calculations of the OKULIX software, which considers anterior and posterior corneal surface.[19] There are no recommendations regarding the superiority of specific calculation formulas.

Toric lenses can be implanted in selected patients with severe astigmatism. However, the unpredictable change in astigmatism caused by DMEK or DSAEK, especially its alignment, should be considered. If bilateral surgery is indicated, the calculation of the second eye can be based on the refractive results of the partner eye.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

CK has disclosed no conflicts of interest. MS is a consultant for Alcon, Oculus, and Zeiss.

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Data Availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

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PERSPECTIVE

Preventive measures for lacrimal procedures during the outbreak of COVID-19: perspective

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Abstract

Aerosols are a major route of transmission of COVID-19. Lacrimal procedures such as lacrimal irrigation, manipulation, and surgery involve aerosols. We searched the PubMed database for articles related to preventive measures of lacrimal procedures during the COVID-19 pandemic. Seven relevant articles were reviewed. Preoperative measures include patient screening, triage, and use of personal protective equipment. Intraoperative measures include procedure-specific aerosol reduction, use of povidone-iodine as disinfectant, and use of personal protective equipment. Postoperative measures include use of telemedicine for follow-up. Elective lacrimal procedures were suspended periodically and resumed when the outbreak subsided, with strict implementation of guidelines. The preventive measures may be effective in lowering the risk of transmission from patients potentially positive with COVID-19.

Key words: Aerosols; COVID-19; Dacryocystorhinostomy; Lacrimal apparatus diseases; Nasolacrimal duct

Background

The Severe Acute Respiratory Syndrome Coronavirus 2 can cause pneumonia and multiorgan disease. Common symptoms include fever, cough, and myalgia. The transmission routes of COVID-19 include direct transmission (via contact of oral, nasal, and ocular mucosa with infected respiratory droplets after coughing and sneezing), airborne transmission (via aerosols during aerosol-generating procedures), and feco-oral transmission (via viral shedding in feces and urine).[1-3] Aerosols are small respirable particles of <5-10 μm that can remain airborne for short- and long-range transport.[4,5] The virus can survive up to 3 hours in aerosols.[6] Patients with COVID-19 may present with ocular symptoms, and shedding of the virus in tears can be detected by reverse transcription polymerase chain reaction.[7-9]

Lacrimal irrigation, manipulation, and surgery involve aerosols.[10] Dacryocystorhinostomy involves manipulation of nasal tissue and lacrimal apparatus, general anesthesia during airway management, and use of ultrasonic aspirators, bone drills, and cautery.[11-14] Preventive measures should be implemented to reduce the risk of transmission. We aim to review the current preventive measures for lacrimal procedures during the COVID-19 pandemic and share our experience in the Department of Ophthalmology of Hong Kong West Cluster.

Methods

The PubMed database was searched on 4 February 2021 using keywords: 'lacrimal surgery', 'lacrimal procedures', 'dacryocystorhinostomy', 'nasolacrimal duct surgery', 'aerosol', and 'COVID-19'. 15 articles were identified and curated for preventive measures of lacrimal procedures during the COVID-19 pandemic. Seven of them were relevant.[15-21] Practices to reduce the spread of the coronavirus during lacrimal surgery include patient screening,[15,18-20] triage and prioritization according to the urgency,[15,17,19-21]

the use of personal protective equipment (PPE),[15,19-21] preventive measures to reduce aerosol generation during lacrimal procedures,[15,17,20,21] the use of povidone-iodine as a disinfectant,[15,16,18] and the use of telemedicine in follow-up.[18-20]

Patient screening

Patients should be screened for the presence of fever, symptoms suggestive of respiratory tract infection, acute conjunctivitis, and diarrhea.[15,18-20] Their travel history, occupation, contact history with suspected or confirmed COVID-19 cases, and personal address should also be recorded.[15,18-20] Those who failed the screening should be isolated, consulted by a doctor, and tested for COVID-19.[20] Patients who need to undergo high-risk procedures (such as endoscopic, endonasal dacryocystorhinostomy) should take serological (immunoglobulins M and G) and reverse transcription polymerase chain reaction tests[17,19,21] and chest radiography[21] before the operation.

Triage and prioritization

Elective high-risk lacrimal procedures should be avoided during the outbreak of COVID-19.[15,17,19-21] According to the Royal Australian and New Zealand College of Ophthalmologists guideline, high infection risk procedures (such as surgery involving upper aerodigestive tract, nasal syringing, sinonasal surgery, and nasal endoscopy) should not be performed unless indicated.[20] Patients requiring nasal or dacryoendoscopy should be triaged to three categories: emergency (congenital dacryocystocele, postsurgical epistaxis, pediatric acute dacryocystitis, acute nasolacrimal duct trauma and suspected recurrence of previous lacrimal drainage malignancy), urgency (recurrent hemolacria, inflammatory secondary acquired lacrimal drainage obstruction, suspected lacrimal drainage mass and stent extubation in presence of complications), and elective (routine primary acquired nasolacrimal duct obstruction, congenital nasolacrimal duct obstruction, uncomplicated stent extubation).[15] Ophthalmologists can decide on the necessity of the procedure and whether it should be postponed or performed early.[17] Emergent lacrimal procedure should be performed regardless of the COVID-19 status of the patient.[15] Those suspected to have COVID-19 and require semi-urgent procedures should be isolated, and the decision on the lacrimal procedure should be made after testing of COVID-19. For patients without any symptoms but have problems answering the questionnaire, infectious disease specialist should be consulted, and COVID -19 test should be performed before the surgery.[15]

Personal protective equipment

Ophthalmologists should use PPE (mask, gloves, glasses, and gowns).[19,20] Protective masks should be worn constantly and changed every 4 hours.[19] The slit lamp should be mounted with a plastic shield.[19,20] There are two PPE variants for lacrimal surgeries: enhanced PPE and full PPE.[15] The enhanced PPE include regular scrubs, full sleeve surgical gown, surgical head cap, N-95/FFP3 respirator, goggles, double surgical gloves, and boot cover, whereas the full PPE include disposable scrubs, double surgical gloves, full sleeve surgical gown with hairnet and hood cover, boot cover, N-95/FFP3 respirator, goggles, and face shield. All India Ophthalmological Society – Oculoplastics Association of India suggest two types of PPE: type A (ideal PPE) and type B (minimum PPE).[21] Ideal PPE include hazmat suit, N95, shoe cover, and visor, whereas minimum PPE include surgical gown, N95, visor, and shoe cover, with or without cap, plastic apron, and goggles.

Povidone-iodine as disinfectant

Povidone-iodine can be used as disinfectant in various forms:[15,16,18] eyedrops (1% to 5% concentration), gargles (1%), and throat spray (0.45%).[16] For lacrimal surgeries, a preoperative protocol is suggested: using 1% povidone-iodine gargles, placing 1% povidone-iodine in conjunctival cul-de-sac, irrigating the lacrimal drainage system with 0.4% povidone-iodine, and placing 0.4% povidone-iodine in the anterior nasal cannula.[16]

Reducing aerosol generation and transmission

Methods to reduce aerosol generation and transmission during lacrimal surgeries are suggested.[15,17,20,21]

Intraoperative measures

For lacrimal irrigation, All India Ophthalmological Society – Oculoplastics Association of India suggest that all staff should wear minimum PPE and use low capacity 1-cc syringe and 25- or 27-G straight cannulas. Using a probe to assess obstruction should be avoided.[15]

For nasal and dacryoendoscopy, all surfaces of endoscopy-procedure room should be cleaned systemically.[17] The number of staff should be minimized, and staff should wear PPE. The procedure should be quick and under control. To keep a distance from the patient, magnifiers or loupes should be used. Direct viewing through eyepiece of endoscopy should be substituted by using a monitor. After the procedure, instruments should be sterilized, and contaminated disposables should be disposed. The use of atomizers and suction should be avoided, as should routine nasal endoscopy.[15]

Elective dacryocystorhinostomy should not be performed,[15,21] because drills and debriders increase the chance of aerosol generation when removing bone within nasal cavity.[21] During endoscopic dacryocystorhinostomy, all staff in the operation theater should wear PPE.[21] External route is preferred when an urgent dacryocystorhinostomy is needed.[15] Powered instruments such as cautery, drills, ultrasonic aspirators, and suction should not be used.[15,21] Incisional blades should be used instead.[15] Direct decongestion on nasal mucosa is needed before incision to prevent the requirement of suction.[15]

Local anesthesia is preferred to general anesthesia.[20,21] Intubation in general anesthesia may generate aerosols and expose anesthesiologists to patients' respiratory secretions.[20,21] Only anesthetic staff should be present

during intubation.[20] Fentanyl or alfentanil should be used for sedation to avoid sneezing reflex during periocular anesthetic injection.[20]

For stent extubation, endoscopic removal is the quickest way, but external approach can also be used.[15] The sneezing maneuver is not recommended during the external approach.[15] When the sneezing maneuver is required, patient should be instructed to blow their nose away from others after the stent is divided between the puncta.[20] Bicanalicular stents can be removed through the conjunctival aspect.[20]

Telemedicine

Telemedicine may be used by oculoplastic surgeons during follow-ups.[18-20] Telephone encounters, video visits, meeting platforms, and telemedicine-enabled slit lamps can be used.[18] To facilitate telemedicine in follow-up, dissolvable skin sutures should be used.[20] However, telemedicine cannot be used in patients without internet connection and when physical examination is required.[20] Quarantined physicians can take up the role of telemedicine to reduce the workload of practicing physicians.[18]

Discussion

In Hong Kong West Cluster, elective lacrimal procedures were suspended periodically and resumed when the outbreak subsided, with strict implementation of guidelines. There has been no COVID-19 case secondary to lacrimal procedures.

To reduce the risk of COVID-19 transmission, the Hong Kong West Cluster implement several preventive measures. Surgical masks and gloves are used during probing and irrigation. Patients for endoscopic procedure and/or dacryocystorhinostomy must obtain negative COVID-19 test results before dacryoendoscopic assessment of the nasal anatomy. Ophthalmologists are equipped with full personal protective equipment (gloves, gowns, face shields) and N95 respirators, as endoscopy is considered an aerosol-generating procedure. Another COVID-19 test is required before dacryocystorhinostomy, which is performed under general anesthesia. N95 respirators and surgical gowns are used during the operation. All medical personnel involved are required the same protective standard. Minimal medical personnel are allowed in the operation theater. Bicanalicular stent is used. Strict restrictions are applied during nasoendoscopic procedures for clot removal, checking of the osteotomy site, ensuring the postoperative patency of the drainage tract, and stent removal. Both stent and clot were removed via the nasal route with the nasoendoscope.

Conclusion

Various pre-, intra-, and post-operative preventive measures may help reduce the risk of transmission of COVID-19. In Hong Kong West Cluster, there has been no COVID-19 case secondary to lacrimal procedures.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Data Availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

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CASE REPORT

Diagnostic pitfall of progressive isolated abducens nerve palsy: a report of two cases

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Abstract

We describe two cases of progressive abducens nerve palsy secondary to a compressive lesion in the Dorello canal. Blood tests, lumbar puncture, nasopharyngeal examination, computed tomography, magnetic resonance imaging, and angiography were performed, but the etiology could not be identified. After consultation with a neuroradiologist, fine-cut magnetic resonance imaging along the course of the abducens nerve with gadolinium and constructive interference in steady state sequences was performed, and the diagnosis was made. In cases of small intracranial pathology, the use of thinner slices or specific sequences is suggested to better visualize the course of cranial nerves.

Key words: Abducens nerve; Cranial nerve palsy; Magnetic resonance imaging

Case presentation

Patient 1

In 2010, a 49-year-old woman with hypertension presented with a 2-week history of acute onset binocular horizontal diplopia. Clinical examination revealed isolated right eye abduction defect. Blood tests showed hypercholesterolemia only. Results of computer tomography of the brain and orbits and magnetic resonance imaging (MRI) of the brain were non-contributory. A preliminary diagnosis of right abducens nerve (CN6) palsy of microvascular origin was made. The patient was then started on aspirin and simvastatin, but the CN6 palsy progressed in the following months. Tests for thyroid eye disease and myasthenia gravis, lumber puncture, ear, nose and throat examination, repeated MRI with gadolinium, and angiography of the brain and neck (reviewed with neuro-radiologists and neurologists) showed no causative lesion. After consultation with a neuroradiologist, fine-cut MRI along the course of CN6 with gadolinium and constructive interference in steady state (CISS) sequences was performed 8 months after symptom onset. A 0.9×0.9×0.9 cm enhancing extra-axial lesion was identified at the right retro-clival region, situating at the Dorello canal in the vicinity of CN6, suggestive of a nerve sheath tumor or meningioma (**Figure 1**). She underwent craniotomy with tumor excision and then stereotactic radiosurgery for residual tumor and strabismus surgery for symptomatic relief. The pathology of the lesion was meningioma. At the 6-year follow-up, MRI of the brain showed a residual tumor of 0.6×0.9×0.9 cm at the right petroclival region, with no significant interval change.

Patient 2

In 2019, a 20-year-old woman presented with a 1-year history of painless progressive binocular horizontal diplopia. Clinical examination revealed isolated left eye abduction defect. Results of computed tomography of the

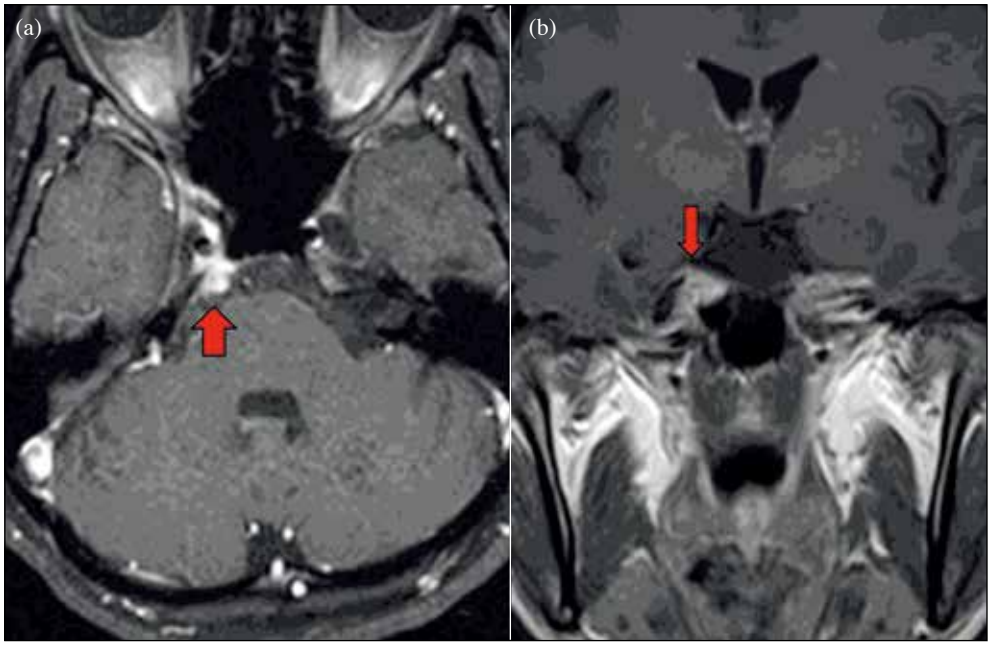

Figure 1. Patient 1: (a) Axial and (b) coronal T1-weighted high-resolution fat-suppressed post-gadolinium contrast magnetic resonance images along the course of abducens nerve revealing a 0.9×0.9×0.9cm contrast-enhancing extra-axial mass (arrows) at the right retroclival region along the course of Dorello canal.

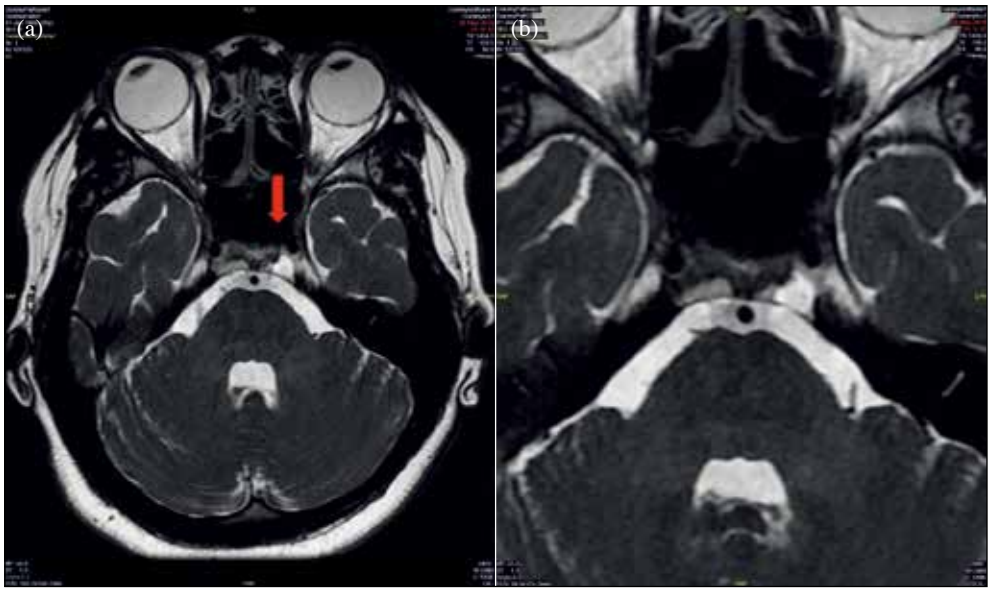

Figure 2. Patient 2: (a) Axial T2-weighted 3D turbo spin-echo sequence magnetic resonance images along the course of abducens nerve revealing a 0.5×0.6 cm non-enhanced mass (arrow) at the left Dorello canal. (b) Post-contrast image does not show the lesion well; the lesion's cystic nature with T1 hypointense signal is similar to the adjacent normal bone marrow.

brain and MRI of the brain, orbits, and internal acoustic meatus with contrast (reviewed by neuro-radiologist) were unremarkable. Further extensive investigations were non-contributory. However, the left CN6 palsy was progressive. After consultation with the neuro-radiologist, a fine-cut MRI along the course of CN6 was performed 4 months after presentation. A focal T2-hyperintense, T1-hypointense signal was identified in the dorsal aspect of clivus involving left Dorello canal, which was only visible in the fine cut of 3D volumetric acquisition using turbo spin-echo with submillimeter section thickness (**Figure 2**). There was no mass effect or contrast enhancement. The signal was not suppressed on fat suppression sequence. Corresponding bony lucent changes in the clivus were retrospectively noted in the initial computed tomographic scan. The lesion involved the left Dorello canal and hence may be accountable for the symptoms. The lesion (0.55×0.6 cm) had a well-demarcated border with no extraosseous soft tissue or aggressive bone destruction, which was likely to be a benign notochordal cell tumor. Differential diagnoses include arachnoid cyst, red marrow deposition, and ecchordosis physaliphora. The patient was referred to the neurosurgical unit and opted for

observation. At the 2-year follow-up, she was coping with a combination of Fresnel prism and head posturing.

Discussion

The CN6 is the most frequently affected ocular motor cranial nerve[1] and is susceptible to injury along its course from the pons to the orbits. The prevalence and etiologies of isolated CN6 palsy vary across different age groups. In a Japanese cohort, most cases were attributed by microvascular origin (35.9%) and neoplasm (22.2%), but the most frequent cause was head trauma and congenital in patients of age <20 years.[1] In patients aged 20 to 49 years, 44% of cases were attributed to an intracranial organic lesion such as aneurysm, neoplasm, or arteriovenous malformation.[1] In those aged ≥50 years, microvasculopathy accounts for most cases.[1,2] Despite advances in modern imaging techniques, causes remained undetermined in 22% to 30% of cases.[2]

We demonstrated a diagnostic pitfall in patients with isolated CN6 palsy. Close monitoring without neuroimaging is advocated in patients aged ≥50 with isolated CN6 palsy and cardiovascular risk factors,[3] as most will improve spontaneously by 6 months.[1] However, controversies remain regarding prompt versus delayed neuroimaging, as pre-existing vasculopathic risk factors do not preclude intracranial neoplasm. Adequate follow-up is crucial for isolated CN6 palsy of presumed microvascular etiology. However, prompt neuroimaging is recommended for patients of young age or without identifiable vasculopathic risk factors. MRI is recommended if the nerve palsy progresses or should additional neurological sign emerge.

We highlighted the importance of choosing the correct scanning sequence and communication with neuroradiologists. MRI is preferred; CT is complementary in cases with suspicion of a bone or skull base lesion or with contraindication for MRI. Intravenous administration of gadolinium is essential in detecting small enhancing lesions of nerves, whereas leptomeningeal/dural/carvenous sinus enhancement may indicate an inflammatory or neoplastic lesion.[2] Apart from fat saturation technique, a heavily T2-weighted sequence, usually a 3D turbo or fast spin-echo sequence (SPACE or CUBE) with submillimeter section thickness or a balanced steady-state free-precession sequence (such as constructive interference in steady state sequence or fast imaging employing steady-state acquisition) should also be performed.[4,5] Although there is no standardized imaging technique for the cisternal part of CN6, the use of pre-contrast constructive interference in steady state sequence / fast imaging employing steady-state acquisition and post-contrast 3D turbo or fast spin-echo to evaluate this part of the abducens nerve that traverses the Dorello canal is recommended.[5]

Though rare, neoplasm of the Dorello canal may present as isolated progressive CN6 palsy. In cases with no abnormality found, we suggest consultation with neuroradiologists before concluding the cases as idiopathic. When suspicion of intracranial pathology remains high, repeat imaging with thinner slices or specific sequences is suggested to better visualize the course of cranial nerves. Appropriate neuroimaging prevents unnecessary investigations, which are potentially invasive or costly.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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All authors have disclosed no conflicts of interest.

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Data Availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

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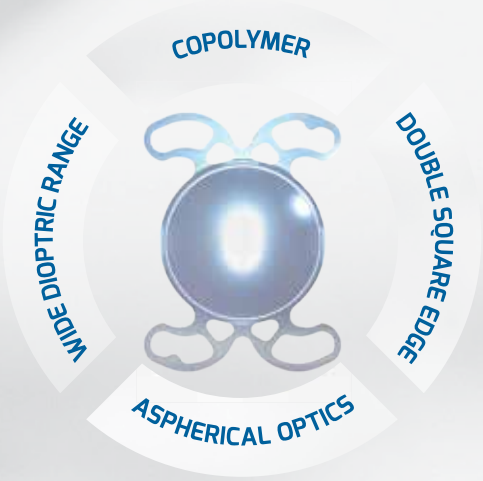

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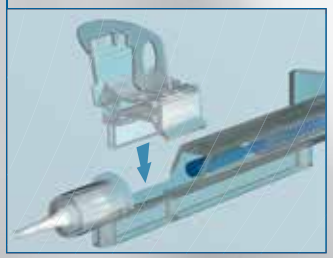
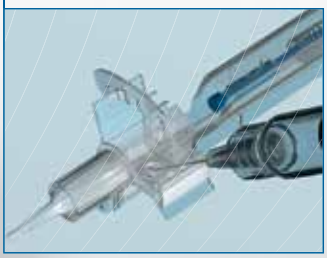
INSTRUCTION FOR USE OF THE PRELOADED VERSION

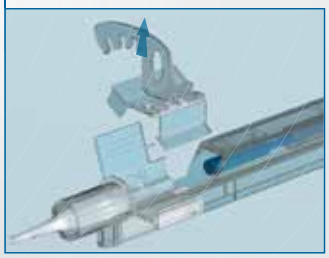
1. Insert the cartridge, containing the IOL, into the injector.



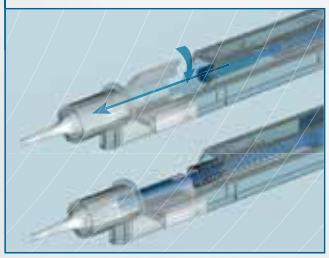
2. Apply viscoelastic solution first through the front hole (until is filled) and then a little through the rear hole.



3. Remove the clip of safety block by lifting it using your index and thumb fingers.



4. Close the cartridge sides together until the "click-lock" mechanism engages. Push forward the plunger softly and ensure that the silicone cushion correctly enters into the cartridge loading chamber.



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AffaMed Technologies is the joint venture established between AffaMed and SIFI, to develop, manufacture and commercialize premium intraocular lenses (IOLs) in the Greater China market.

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