CLINICAL INSIGHTS IN EYECARE

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A JOURNAL *of the* AMERICAN ACADEMY *of* OPTOMETRY

FEATURED INSIGHT

CASE SERIES: NEUROPLASTICITY AND VISION THERAPY IN ADULTS WITH UNILATERAL SMALL-ANGLE ESOTROPIA

Photo credit: Silvia Han, OD, FAAO

A CASE REPORT OF PARIETAL LOBE GLIOBLASTOMA AND POST-SURGICAL NEUROSENSORY DEFICITS

CASE REPORT: NEUROTROPHIC ULCER SECONDARY TO A HYPOPLASTIC TRIGEMINAL NERVE IN A BOY AGED 3 YEARS

CASE REPORT: CORNEAL ULCERATION ASSOCIATED WITH DUPILUMAB

CLINICAL INSIGHTS IN EYECARE
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Editorial

Journal Editorial

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Clinical Insights in Eyecare
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Welcome to the April issue of ***Clinical Insights in Eyecare***. This issue includes 4 interesting case reports/series. The Case Series: Neuroplasticity and Vision Therapy in Adults with Unilateral Small-Angle Esotropia by Silvia Han, Jeffrey Baker, and Erin Jenewein is featured on our cover. They present 3 interesting case reports of adults with unilateral esotropia who achieved random dot stereopsis with vision therapy. These 3 cases highlight the success that can be attained in motivated adult patients when visual therapy is used. This suggests neuroplasticity continues even through adult life. Vision therapy can facilitate this process in adult patients with longstanding strabismus to achieve stereopsis.

This issue has 3 additional case reports. One of the reports describes the use of neurotization (nerve grafting), an indirect interpositional technique, in a child aged 3 years with a neurotrophic cornea/ulcer secondary to a hypoplastic trigeminal nerve. Multiple topical therapies were used to treat the recalcitrant ulcer and provided short-term relief. It's fascinating to think about retrograde neuronal restoration of the trigeminal nerve from the rerouted sural donor nerve graft. A timely patient-focused therapy is crucial to minimize the potential risk of corneal infection. Read this challenging case report to learn more about this effective surgical remedy for neurotrophic keratopathy.

Another one of the case reports highlights the ravaging morbidity and high mortality rate with glioblastomas due to its unfortunate daily growth rate. This report describes visual field defects and hallucinations associated with this parietal lobe brain tumor. Surgical resection is associated with its own morbidity and dysfunction impairing neurosensory function.

Our last case report in this issue describes the potential for adverse events in patients with atopic disease taking the monoclonal antibody, dupilumab. Dupilumab is a fully human monoclonal immunoglobulin G antibody that blocks the shared interleukin 4 and interleukin 13 receptor, thus having a direct effect on the ocular surface ecosystem and in particular, goblet cells. Dupilumab is a highly effective treatment for atopic diseases and, in many instances, can still be used with careful monitoring for adverse ocular surface changes. The authors carefully point out that the exact mechanisms in which dupilumab causes or exacerbates ocular surface disease is yet to be determined.

This issue's provocative question in our Point/Counterpoint is presented by the Retina Special Interest Group. Jessica Haynes and Rachel Steele from the Charles Retinal Institute in Memphis, TN, examine treatment options for the patients who have moderately severe to severe nonproliferative retinopathy without significant macular edema. Until recently, this group has been excluded from the treatment protocols. Recent evidence has shown some improvement in the Diabetic Retinopathy Severity Score (DRSS) and a decreased risk of sight-threatening complications in diabetic patients with moderately severe or severe nonproliferative retinopathy who lack center-involved macular edema treated with intravitreal antivascular endothelial growth factors. Controversy exists regarding any long-term benefits as it relates to the proper endpoints and the concerns for potential rebounds from abruptly stopping the injections.

Once again, Drew Rixon and Aaron Bonner provide excellent journal scans, pertinent reviews from other publications, for this month's issue. The reviews are chock-full of valuable pearls on several topics that should help us provide better care for our patients.

The Academy thanks all who have submitted case reports and looks forward to receiving many more in the future. Keep them coming! We are striving to always provide a great publication, so we look forward to hearing from you with any suggestions.

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CLINICAL INSIGHTS IN EYECARE
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Case Reports

Case Series: Neuroplasticity and Vision Therapy in Adults with Unilateral Small-Angle Esotropia

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Keywords: vision therapy, esotropia, stereopsis, neuroplasticity

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Introduction

Eyecare providers may hesitate to offer treatment to adults with long-standing constant strabismus, assuming that binocularity will be unobtainable. Adult patients may present with personal goals or symptoms that require treatment for their strabismus to restore binocularity. We report three cases of adults with unilateral small-angle esotropia who achieved random dot stereopsis after optometric vision therapy.

Case Reports

Case one: A 33-year-old man's goal was to improve vision in his left eye and to appreciate virtual reality. He presented with a constant left esotropia and amblyopia with normal correspondence and no random dot stereopsis. After spectacle correction with vertical prism, vision therapy, and 2 hours of daily patching, he was able to appreciate random dot stereopsis and visual acuity of 20/25 in his left eye.
Case two: A 25-year-old woman's goal was to improve vision in her left eye and establish binocularity because she experienced blur while performing slit lamp examination as a result of her eyes "alternating fixation." She presented with a constant left esotropia, amblyopia, eccentric fixation, anomalous correspondence, and no random dot stereopsis. After vision therapy, she was able to appreciate random dot stereopsis and visual acuity of 20/20-1 in her left eye.
Case three: A 25-year-old woman's goal was to reduce headache symptoms and establish binocularity. She presented with an intermittent left esotropia with variable left hypotropia, anomalous correspondence, and no random dot stereopsis. After vision therapy, she was able to appreciate random dot stereopsis.

Conclusion

Although treatment of adult strabismus can be challenging, adults with goals related to binocularity can be successfully treated. These three cases highlight successful vision therapy in motivated adult patients with a goal of binocular vision.

INTRODUCTION

Neuroplasticity is the ability of the nervous system to adapt and change in response to different stimuli and experiences, which involves strengthening some synaptic connections while eliminating others.[1] This process is most robust during the critical period, which varies for different functions.[1] It was previously thought that neuroplastic changes were restricted to that period[2] and skills would be permanently affected if they failed to develop during that time.[3] The critical period for development of stereopsis is defined to be 3 months to at least 3 years of age.[4] Disruption of visual input can affect the development of binocularity, specifically stereopsis, in individuals with strabismus. For esotropia, the period in which stereopsis is susceptible to anomalous binocular vision was found to be soon after birth to at least 4.6 years of age.[4]

The misconception of limited improvement with treatment beyond the critical period may prevent adults from seeking treatment for their strabismus or deter health care professionals from recommending treatment, including vision therapy and strabismus surgery.[5] There is growing evidence that neuroplasticity is possible in adults past the critical period of visual development. This is evident by improved binocularity in adults with strabismus after surgery,[5-10] improved amblyopic eye visual acuity in adults with patching and binocular therapy,[11] and improved oculomotor skills in adults with vision therapy.[12,13] However, there is limited research on the use of vision therapy to restore binocularity in adults with strabismus, as most reports are restricted to case studies.[14-19] Although most

adult patients with long-standing strabismus do not experience symptoms, these patients may have cosmetic concerns, occupational goals, or personal goals that require alignment or binocular vision. In these cases, treatment of the strabismus may improve these patients' quality of life[5-7] by improving visual function.

The prognosis for successful treatment of strabismus depends on several factors, including, but not limited to, the presence of a sensory fusion anomaly, direction, size, and time of onset of the strabismus.[20-22] Amblyopia can also add another layer of treatment complexity. Adult patients with strabismus desiring binocular vision may be offered various treatment options, including vision therapy. The goal of vision therapy is to eliminate sensory anomalies and improve sensory and motor fusion with the hope that this leads to improved binocularity. This case series describes adults with constant unilateral small-angle esotropia who achieved their goals of binocular vision through vision therapy. No identifiable health information was included in this case series.

CASE REPORTS

CASE 1

A 33-year-old man presented with a complaint of long-standing reduced vision in his left eye and an inability to appreciate virtual reality. His goal was to improve vision and to appreciate virtual reality. Ocular history included amblyopia with poor adherence to patching therapy during childhood.

Distance visual acuities (electronic Early Treatment Diabetic Retinopathy Study [E-ETDRS]) through his presenting spectacles were right eye -1.25 sphere (20/20, letter score 88), left eye Plano sphere (20/50, letter score 65). Interferometry using a Heine Retinometer showed identification of 20/30 grating targets (left eye). Cycloplegic autorefraction, using 2 drops of 1% cyclopentolate, was right eye +0.37 - 0.50 × 170, left eye +6.12 - 1.50 × 009. Cycloplegic manifest refraction and visual acuities (Snellen) were right eye Plano sphere (20/20), left eye +6.50 - 0.50 × 180 (20/125). Because the patient had not worn a full anisometropic prescription, he was recommended to return 1 week later to finalize his spectacle prescription. Through cycloplegic manifest refraction, he experienced dizziness and diplopia. Anisometropic prescription, through trial framing, was consequently reduced. In a trial frame, the following prescription was most comfortable and recommended for full-time wear: right eye Plano sphere, left eye +5.75 - 0.50 × 015 (Snellen 20/100).

After the patient adapted to the spectacle prescription for 1 month, a strabismus evaluation (Table 1) was performed. The patient reported diagonal diplopia on Worth four-dot and synoptophore testing. Second-degree fusion was not achieved on Worth four-dot with neutralizing prism, but it was achieved during synoptophore testing at his subjective angle. Vertical prism was trial framed based on his subjective angle, and 5Δ was most comfortable, so his spectacles were remade to include right eye 2.5Δ base-down, left eye 2.5Δ base-up. Contact lenses were considered to reduce potential aniseikonia, but the patient did not want contact lenses and the amount of vertical prism was too high for contact lenses.

The patient was diagnosed with microtropia and mixed mechanism (strabismic and anisometropic) amblyopia in his left eye. Prognosis for strabismus treatment was guarded, in which a favorable prognostic factor includes normal correspondence and unfavorable prognostic factors include esotropia and amblyopia. The patient was motivated to achieve his visual goals, and in-office 45-minute weekly vision therapy was recommended. Home therapy (15-20 minutes daily) with 2 hours of patching (right eye) during near activities was prescribed. Vision therapy focused on developing binocularity by reducing the frequency of his esotropia and improving vision in his left eye. Base-out prism was discussed, but he wanted to try vision therapy first. Strabismus surgery was not recommended owing to the esotropia being a small angle, and the risk outweighed the benefits.

The patient's vision therapy program progressed from improving monocular visual function, to establishing normal peripheral then central fusion, to—lastly—establishing efficient binocular vision in open space. Vision therapy activities (Table 2) were categorized into monocular visual skills, vergence, and antisuppression training. The beginning of the program aimed at normalizing accommodative and oculomotor skills in the left eye. Accommodative techniques were first performed monocularly, starting with increasing accommodative amplitude and awareness and then moving on to facility. Monocular gross saccades were trained first, then progressing to medium and fine saccades. Form discrimination therapy was also included. These visual skills were later integrated with vergence training.

Given the constant nature of the patient's strabismus but normal sensory fusion at his objective angle, divergence training was performed from his objective angle[22] in the synoptophore and Wheatstone stereoscope. Antisuppression therapy was incorporated to reduce suppression and develop pathological diplopia awareness when he was strabismic. When he achieved fusion at orthoposition, out-of-instrument divergence training at near using vectograms and Tranaglyphs was initiated. Computer vergence therapy (Vision Therapy System 4) with random dot stereopsis targets of 600" was used to help him appreciate stereopsis. Convergence training was gradually incorporated. During the last stage, vergence training advanced from near to intermediate and then far distances.

After 30 sessions and daily patching, the patient's amblyopic eye visual acuity improved to 20/25 and he could appreciate random dot stereopsis of 250". In addition, the frequency of his esotropia changed from constant to intermittent. Although base-out prism could be beneficial in stabilizing his binocularity, he elected not to proceed with this treatment because he already attained his goal. Patching was tapered (3 days per week for the first month, 2 days per week for the second month, and 1 day per week for the third month) before discontinuing, and home maintenance therapy was prescribed.

Table 1. Examination findings before and after vision therapy for case 1

Tests	Initial Evaluation	Post–Vision Therapy Evaluation
Best-corrected distance visual acuity	Right eye: Plano sphere (E-ETDRS 20/16, letter score 93) Left eye: +5.75 - 0.50 × 015 (E-ETDRS 20/100, letter score 49)	Right eye: Plano sphere with 2.5Δ base-down (E-ETDRS 20/16, letter score 93) Left eye: +5.75 - 0.50 × 015 with 2.5Δ base-up (E-ETDRS 20/25, letter score 81)
Monocular fixation	Visuoscopy: central, steady (right and left eye)	
Cover test (with correction)	Far: 6Δ constant left esotropia with 4Δ constant left hypotropia Near: 10Δ constant left esotropia with 4Δ constant left hypotropia	Far: 2Δ intermittent left esotropia (70%) Near: 8Δ intermittent left esotropia (80%)
Comitancy	Cover test in diagnostic action fields: comitant eso- and vertical deviation	
Extraocular movement test	Full range of motion, right and left eyes	
Correspondence	Synoptophore: normal correspondence	
In-instrument evaluation of sensorimotor fusion	Synoptophore: stable second-degree peripheral and central fusion at objective angle (15Δ base-out with 6Δ left hypotropia); inadequate motor fusion from objective angle	
Out-of-instrument evaluation of sensorimotor fusion	Worth four-dot Far and near: uncrossed and vertical diplopia (unable to achieve fusion with neutralizing base-out and base-down prism over the right eye) Stereopsis Far: nil (Distance Randot Stereotest) Near: nil (Randot Stereotest) [a]with and without neutralizing prism	Worth four-dot Far: uncrossed diplopia Near: alternates between fusion and uncrossed diplopia Stereopsis Far: nil (Distance Randot Stereotest) Near: 250" random dot stereopsis (Randot Stereotest) Motor Ranges (from ortho) Far: divergence x/1/0; convergence x/20/16 Near: divergence x/2/1; convergence x/20/18

[a]Far and near stereopsis.
E-ETDRS, electronic Early Treatment Diabetic Retinopathy Study.

At the 3-month post–vision therapy progress evaluation, the patient still retained random dot stereopsis. Refraction remained unchanged, but left eye visual acuity regressed to 20/40 (letter score 73). To the authors' knowledge, there are no studies regarding regression in amblyopic eye visual acuity in adults, but research in children shows that regression can occur after discontinuing treatment when amblyopic eye visual acuity significantly improves or treatment is initiated at an older age.[23] Contact lenses were discussed, but he preferred spectacles. It was recommended that he restart patching 1 hour a day and return in 2 months for a follow-up, but he was lost to follow-up.

CASE 2

A 25-year-old woman presented with a complaint of blurred vision while performing slit lamp examination as a result of her eyes "alternating fixation." Ocular history included amblyopia in her left eye with good adherence to patching therapy during childhood. Her goals were to resolve her amblyopia and develop stereopsis.

Distance visual acuities (Snellen) through her spectacle correction (+4.00 sphere both eyes) were 20/20 right eye, 20/30 left eye. A previous cycloplegic refraction revealed +5.50 sphere both eyes, but the patient reported discomfort with that prescription. Noncycloplegic manifest refraction of +4.75 sphere both eyes was found, trial framed, and finalized for full-time wear; it was well tolerated and distance visual acuity was unaffected.

Strabismus and amblyopia evaluation findings are listed in Table 3. Cover test revealed a comitant constant left esotropia of 4Δ at distance and 2Δ at near. She was found to have harmonious anomalous correspondence, 1Δ of nasal eccentric fixation in the left eye, and no random dot stereopsis. The patient was diagnosed with microtropia and strabismic amblyopia in her left eye. She was offered patching therapy alone to treat her amblyopia or patching with vision therapy to treat both amblyopia and strabismus. Her prognosis for strabismus treatment was guarded, where esotropia, anomalous correspondence, and amblyopia with eccentric fixation are unfavorable prognostic factors. Strabismus surgery was not recommended owing to the small size of her angle. Prism was contraindicated because of the presence of anomalous correspondence.

The patient was motivated to achieve her goals and elected weekly 45-minute in-office vision therapy, including 10-15 minutes of daily home therapy. The main objective of therapy was to improve vision in her left eye, as well as eliminate anomalous correspondence and develop binocularity. The vision therapy activities (Table 4) were categorized into monocular visual skills and vergence training. The beginning sessions focused on eliminating ec-

Table 2. Vision therapy activities (in-office in addition to home vision therapy) for case 1

Monocular Therapy		Vergence Therapy		Antisuppression Therapy	
Visits	**Subskill and Activities**	**Visits**	**Subskill and Activities**	**Visits**	**Subskill and Activities**
1-5	Accommodative amplitude and awareness • Hart chart push-ups • Lens clearing (+2 to -6 lenses) Accommodative facility • Near-far Hart chart rock • Accommodative rock with flippers Saccades (medium and fine) • Hart chart saccades with after-image • Letter tracking Form discrimination • Hidden pictures	1-10	Vergence awareness • Brock string with red-green glasses Motor stimulation • Synoptophore (Flom swing) BI Smooth vergence at near • Wheatstone BI • Vectograms/ Tranaglyphs BI • VTS4 (vergence setting, flat fusion target) BI • VTS4 (vergence setting, lateral disparity stereopsis target) BI	1-5	• Brock string with red-green glasses
6-15	Saccades (fine) • Line counting • Percon saccades • Visual scan • Perceptual speed worksheets Accommodative awareness • Lens sorting • Mental Minus	11-15	Smooth vergence at near • Vectograms/ Tranaglyphs BI and BO • VTS4 (vergence setting, lateral disparity stereopsis target) BI and BO • VTS4 (multiple choice, large RDS target) BI and BO Step vergence at near • Step Vectograms/ Tranaglyphs BO and BI • VTS4 (multiple choice, large RDS target) BI and BO step vergences • Aperture Rule Trainer BI and BO Binocular accommodative facility • Binocular accommodative facility with flippers	6-10	• Single oblique stereoscope (cheiroscope) • GTVT chart at near, then distance • Honeycomb chart at near, then distance • Sanet Vision Integrator with red-blue glasses • VTS4 cheiroscope • Red coloring book tracing • Red filter over reading material
16-20	Saccades (medium and fine) • Loose prism saccadic jumps Saccades and accommodative stamina • Letter tracking with minus lenses • Line counting with minus lenses Form discrimination • C-ring directionality	16-20	Step vergence at near • Eccentric circles BI and BO Facility vergence at near • Eccentric circles facility • Vectograms/ Tranaglyphs facility • VTS4 (multiple choice, medium and small RDS target) jump ductions Binocular	11-15	• Red-red rock • Bi-ocular spirangle • Red-green TV trainer at near

			accommodative facility • Binocular accommodative facility with flippers		
21-30	Accommodative stamina • Reading at near with minus lenses Form discrimination • Amblyopia iNet	21-30	Facility vergence at near • Prism flips Vergence at far • VTS4 (multiple choice, small RDS target) BI and BO at 5 and 10 feet • Eccentric circles BI at 5 feet, walk-aways • Brewster BI and BO • TV trainer/GTVT (step BI and BO) at 5 and 10 feet	16-20	• VTS4 amblyopia (red line tracing) • Red X's and O's
Home maintenance	Monocular near-far Hart chart (3 times a week for first month, 2 times a week for second month, 1 time a week for third month)	Home maintenance	Eccentric circles—facility at near and BI at distance (3 times a week for first month, 2 times a week for second month, 1 time a week for third month)		

BI, base-in; BO, base-out; RDS, random dot stereopsis; VTS4, Vision Therapy System 4.

Table 3. Examination findings before and after vision therapy for case 2

Tests	Initial Evaluation	Post–Vision Therapy Evaluation[a]
Best-corrected distance visual acuity	Right eye: +4.00 sphere (Snellen 20/20) Left eye: +4.00 sphere (Snellen 20/30)	Right eye: +4.75 sphere (Snellen 20/20) Left eye: +4.75 sphere (Snellen $20/20^{-1}$)
Monocular fixation	Visuoscopy: 1Δ nasal, unsteady eccentric fixation (left eye) Haidinger's brush: 1Δ nasal eccentric fixation (left eye)	
Cover test (with correction)	Far: 4Δ constant left esotropia Near: 2Δ constant left esotropia	
Comitancy	Cover test in diagnostic action fields: comitant esodeviation	
Extraocular movement test	Full range of motion, right and left eyes	
Correspondence	Worth four-dot: harmonious anomalous correspondence Bagolini striated lenses: harmonious anomalous correspondence Hering-Bielschowsky After-Image test: harmonious anomalous correspondence Synoptophore: harmonious anomalous correspondence	
Out-of-instrument evaluation of sensory fusion	Stereopsis Near: nil (Randot Preschool Stereotest)	Stereopsis Near: 400" random dot stereopsis (Randot Preschool Stereotest)

[a]Patient did not complete entire vision therapy program (only completed 10 sessions).

centric fixation in the left eye and improving accommodative skills. After achieving $20/20^{-1}$ left eye in three visits, motor stimulation using Flom's swing technique in the synoptophore was performed to diverge to an ortho eye alignment. Computer vergence therapy with random dot stereopsis targets was used to help her appreciate stereop-

Table 4. Vision therapy activities (in-office in addition to home vision therapy) for case 2

Monocular Therapy		Vergence Therapy	
Visits	**Subskill and Activities**	**Visits**	**Subskill and Activities**
1-10	Accommodative amplitude and facility • Near-far Hart chart rock • Accommodative rock with flippers Eccentric fixation (fast pointing) • Dotting O's • Stationary pegboard • Haidinger's brushes	1-5	Smooth vergence at near • VTS4 (vergence setting, flat fusion) BI Motor stimulation • Synoptophore (Flom swing) BI
		6-10	Smooth vergence at near • Quoit Vectograms with Marsden ball, BI • VTS4 (multiple choice, large RDS) BI and BO • Quoit and clown Vectograms BI and BO
Home maintenance[a]	Near-far Hart chart rock Accommodative rock with flippers Fast pointing Dotting O's		

[a]These activities were assigned at the 10th vision therapy visit; patient did not return for progress evaluation.
BI, base-in; BO, base-out; RDS, random dot stereopsis; VTS4, Vision Therapy System 4

sis. Vectograms were also incorporated during divergence training in open space.

The patient had to discontinue vision therapy because she relocated from the area. However, after 10 sessions, her visual acuity normalized to $20/20^{-1}$ in the left eye and she was able to appreciate random dot stereopsis of 400". The patient has not returned to the area, so some examination findings could not be reevaluated.

CASE 3

A 25-year-old woman presented with a complaint of pain over her right eye that worsened with extended near work or driving for a long time. It started 2 years ago and did not improve with pain medication. Previous medical records revealed a history of partially accommodative esotropia since age 2 and no stereopsis. Systemic history included type 1 Chiari malformation without ocular manifestations. Her goals were to reduce headache symptoms and establish binocularity.

Distance visual acuities (Snellen) were 20/15 in each eye through contact lenses (right eye +1.75 sphere; left eye +1.50 sphere). Cover test revealed a comitant, high-frequency intermittent left esotropia of 4Δ with asymmetric dissociated vertical deviation and variable left hypotropia of 4Δ at far and near. Her accommodative amplitude and facility were normal in each eye. On the prism adaptation test, she adapted to both horizontal and vertical prism. Additional examination findings from the strabismus evaluation are listed in Table 5.

She was diagnosed with microtropia with left hypotropia and harmonious anomalous correspondence. Prognosis was guarded for improvement of headache symptoms and poor for binocularity. Her unfavorable prognostic factors for strabismus treatment include esotropia, vertical deviation, and anomalous correspondence. Strabismus surgery was not recommended owing to the size of her angle. Prism was contraindicated because of anomalous correspondence and a positive prism adaptation test. After a discussion on the guarded prognosis, she elected to start vision therapy, weekly 45-minute in-office sessions, to see whether her symptoms would improve.

The main objective of vision therapy was to eliminate anomalous correspondence and establish normal correspondence. The vision therapy activities (Table 6) were categorized into monocular visual skills and vergence training. The initial therapy sessions focused on motor stimulation using Flom's Swing technique in the synoptophore, along with enhancement of monocular accommodative skills. Once she began displaying covariation, in- and out-of-instrument vergence (convergence, divergence, and vertical vergence at near and distance) training were introduced. After-images were used to monitor correspondence. On computer therapy, large random dot stereopsis targets were initially used, and target size was decreased over time. She would occasionally use vertical prism (4-5Δ base-down right eye) in-office to help with fusion but did not desire a prism prescription for full-time wear.

After 26 weeks of vision therapy, the patient had to discontinue because she was moving out of the area but was given home maintenance therapy. She could appreciate random dot stereopsis of 250" and noted a significant improvement in headaches following therapy and a difference in her binocular depth perception. The patient has not returned for follow-up, so some examination findings could not be reevaluated.

DISCUSSION

This case series offers some support that neuroplasticity continues through adulthood, and optometric vision therapy can facilitate this process. With vision therapy, all three patients gained the ability to appreciate stereopsis. These cases show that the visual system can be trained and improved after the critical period in adult patients with unilateral small-angle esotropia who never appreciated stereopsis.

The cases detail vision therapy in three patients with microtropia. Intractable diplopia may occur with vision ther-

Table 5. Examination findings before and after vision therapy for Case 3

Tests	Initial Evaluation	Post–Vision Therapy Evaluation[a]
Best-corrected distance visual acuity	Right eye: +1.75 sphere (Snellen 20/15) Left eye: +1.50 sphere (Snellen 20/15)	
Cover test (with correction)	Far: 4Δ intermittent left esotropia with 4Δ intermittent left hypotropia (high frequency) Near: 4Δ intermittent left esotropia with 4Δ Intermittent left hypotropia (high frequency)	Far: 2Δ intermittent left esotropia with 1-2Δ intermittent left hypotropia (low frequency) Near: 2Δ intermittent left esotropia with 1-2Δ intermittent left hypotropia (low frequency)
Comitancy	Cover test in diagnostic action fields: comitant eso- and vertical deviation	
Extraocular Movement Test	Full range of motion, right and left eyes	
Correspondence	Worth four-dot: harmonious anomalous correspondence Bagolini striated lenses: harmonious anomalous correspondence Hering-Bielschowsky After-Image test: normal correspondence Synoptophore: unharmonious anomalous correspondence	Worth four-dot: alternates between fusion and crossed diplopia at near Bagolini striated lenses: alternates between harmonious anomalous and normal correspondence response Hering-Bielschowsky After-Image test: normal correspondence Synoptophore: normal correspondence
Out-of-instrument evaluation of sensory fusion	Stereopsis Near: nil (Randot Stereotest)	Stereopsis Near: 250” random dot stereopsis (Randot Stereotest)

[a]Patient did not complete entire vision therapy program (only completed 26 sessions).

apy, and this was discussed with all three patients, but they elected to try vision therapy to achieve their goals of improved depth perception. Although it has been reported that patients with microtropia may identify random dot stereopsis of 800", which is considered false positive, on the Randot Preschool Stereotest,[24] the patients in our case series ultimately achieved true random dot stereopsis following vision therapy (250" for cases 1 and 3 and 400" for case 2).

Similar to our case series, a few studies have documented improvement in binocular function in adults with esotropia following vision therapy. A retrospective review looked at adults with esotropia, as well as those with exotropia and vertical strabismus, and found an improvement in stereopsis after vision therapy.[25] Two cases found improvement in binocular function after vision therapy in adults with esotropia,[18,19] but they did not achieve stereopsis. In one case, an adult with esotropia and amblyopia presented with anomalous correspondence and no random dot stereopsis.[18] Divergence training was performed under artificial conditions with a red lens, where the patient had to fuse diplopic images in the dark. He also had to maintain fusion of a target while walking away from it. Accommodative, oculomotor, eccentric fixation, eye-hand coordination, and patching therapies were incorporated. Following vision therapy, the patient’s visual acuity and ability to fuse diplopic images improved, but he was not able to appreciate stereopsis. In another case report, an adult patient with esotropia presented with headaches, eye fatigue, and intermittent diplopia.[19] Vision therapy consisted of antisuppression, accommodative, oculomotor, eye-hand coordination, and vergence training, along with techniques to disrupt anomalous correspondence. Following vision therapy, she demonstrated normal correspondence, perceived stereoscopic depth at her centration point, and subjectively reported less eye fatigue.

The vision therapy programs in the aforementioned cases were similar to our case series, in that they all worked on accommodative and vergence activities. However, vergence training in these case reports did not utilize Flom swing. Flom swing, utilized in cases 2 and 3, is a useful therapy technique because it can eliminate anomalous correspondence in small-angle esotropes through expansion of vergence ranges.[22,26] By inducing fusional vergence, covariation of anomalous correspondence to normal correspondence can be achieved and normal fusion can be established. This may be why the patients in our case series were able to appreciate random dot stereopsis after treatment.

These three patients’ vision therapy programs were sequenced based on treatment guidelines for strabismus[22] and amblyopia.[27] Monocular accommodative therapy and motor stimulation were performed at the beginning of therapy, followed by vergence therapy in open space. However, there were some differences in our patients’ profile and specific therapy activities, which contribute to the limitations of this case series. The patients in cases 1 and 2 had amblyopia, so other monocular (oculomotor and spatial perception) activities were included to improve visual acuity and monocular fixation. Vertical prism was prescribed for case 1, but vertical vergence therapy was incorporated for case 3. Not all patients presented with anomalous correspondence. Lastly, the patients in cases 2 and 3 were lost to follow-up before completing vision therapy, so some examination findings were unable to be reassessed. Despite differences and limitations, this case series show that stere-

Table 6. Vision therapy activities (in-office in addition to home vision therapy) for case 3

Monocular Therapy		Vergence Therapy	
Visits	**Subskill and Activities**	**Visits**	**Subskill and Activities**
1-18	Accommodative amplitude and facility • Near-far Hart chart rock • Accommodative rock with flippers	1-6	Smooth vergence at near • VTS4 (vergence setting, flat fusion target) BI • Vectograms BI Motor Stimulation • Synoptophore (Flom swing) BI
		7-12	Vergence awareness • Brock string Smooth vergence at near • Vectograms (with after-images) BI and BO • VTS4 (multiple choice vergence, large RDS target) BI and BO Smooth vergence at distance • Synoptophore (3rd degree target) BI and BO Step vergence at near • Aperture Rule Trainer (with after-images) BI and BO
		13-18	Smooth vergence at near • Vectograms BI and BO • Vectograms (with Marsden ball) BI and BO • VTS4 (multiple choice vergence, large RDS target) BU and BD Smooth vergence at distance • Synoptophore (third-degree target) BI and BO Facility vergence at near • VTS4 (multiple choice RDS) jump ductions
		19-26	Smooth vergence at near • VTS4 (multiple choice vergence, large RDS target) BI, BO, BU, BD Step vergence at near • Aperture Rule Trainer BI and BO • Eccentric circles BI and BO Facility vergence at near • VTS4 (multiple choice, medium RDS target) jump ductions Vergence at far • VTS4 (multiple choice vergence, large RDS target) BI, BO, BU, BD • Quoits Vectograms BI and BO • Quoits Vectograms BI and BO jumps • Spirangle Vectograms BI and BO
Home maintenance	Binocular accommodative rock (3 times a week for first month, 2 times a week for second month, 1 time a week for third month)	Home maintenance	Eccentric circles—facility at near (3 times a week for first month, 2 times a week for second month, 1 time a week for third month)

BD, base-down; BI, base-in; BO, base-out; BU, base-up; RDS, random dot stereopsis; VTS4, Vision Therapy System 4.

opsis could be achieved with vision therapy in adults with long-standing constant strabismus.

Studies have also shown improvement in binocularity with other forms of treatment in adults.[5-10,28] The use of botulinum toxin[28] to treat strabismus has been reported to develop sensory fusion in adults. Sensory fusion development, with Worth four-dot or stereopsis, is possible in adults with strabismus after strabismus surgery owing to improved motor alignment.[5-10]

CONCLUSION

Although treatment of adult strabismus can be challenging, adults with goals related to binocularity may be successfully treated. These cases demonstrate that vision therapy is a viable treatment option for motivated adults with strabismus who want to achieve binocularity. However, this case series is limited to retrospective case studies and highlights the need for prospective, placebo-controlled, ran-

domized clinical trials, to evaluate the effectiveness of vision therapy as a treatment for adult strabismus. Eyecare providers should consider referring motivated adults with strabismus for treatment.

TAKE HOME POINTS

- Optometric vision therapy is a viable treatment option for motivated adults with long-standing strabismus.
- Stereopsis can be achieved with optometric vision therapy in adults with long-standing constant strabismus.
- Eye care providers should consider referring adults with strabismus for evaluation and treatment.

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CLINICAL INSIGHTS IN EYECARE
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Case Reports

A Case Report of Parietal Lobe Glioblastoma and Post-Surgical Neurosensory Deficits

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Keywords: Parietal lobe, Glioblastoma, Neurosensory deficits, Homonymous hemianopia, Brain tumor, Visual hallucinations

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Introduction

The early diagnosis of malignant glioblastomas depends on the onset of precursory neurological symptoms, including headache and visual disturbances. The parietal lobe is a neuro-center for visual information processing; thus, a proliferating glioblastoma can disrupt the visual pathway circuitry, resulting in visual field defects and disturbances such as hallucinations. Additionally, surgical resection of tumors in the parietal lobe can create neurosensory deficits affecting the patient's quality of life.

Case Report

A 76-year-old man presented with complaints of a progressive headache, complex visual hallucinations, and, on examination, evidence of a neurological visual field defect requiring radiology studies. Neuroimaging revealed a right parietal lobe grade IV glioblastoma, and immunohistochemistry detected an isocitrate dehydrogenase wildtype molecular pattern. He underwent the mainstay of surgical treatment for glioblastoma with adjuvant radiation and chemotherapy three days after neuroimaging confirmation. He reported post-surgical integrated sensorimotor symptoms.

Conclusion

Glioblastoma is a fast-growing, primary brain tumor with a high morbidity rate as migrating tumor cells invade surrounding tissues. Its location in the parietal lobe can disrupt the visual pathway, causing hallucinations and visual field defects. Although visual disturbances from tumor growth may subside after lesion resection, disruption to regional neurons may cause lasting visual, neurosensory, and motor deficits.

INTRODUCTION

Glioblastoma, a grade IV astrocytoma, is a fast-growing brain tumor arising de novo or evolving from astrocytes, the supportive cells in the brain.[1,2] The World Health Organization defines grade IV tumors as mitotically active, necrotic, and malignant. Further, the isocitrate dehydrogenase wildtype grade IV glioblastoma is a mutational state marked by histological hypercellularity, microvascular proliferation, and necrosis.[3,4]

The incidence of glioblastoma is 2-3 cases in 100,000 of the population, which is the highest among malignant brain tumors, accounting for 60 percent of diagnosed cases.[5] A recent single-institution retrospective study of 60 patients found that the overall survival rate was 30 percent at one year and 6.7 percent at two years after a maximum resection followed by chemoradiotherapy and adjuvant temozolomide chemotherapy.[6] Other prognostic data calculated the median survival time of 14.6 months, a 26.5 percent two-year survival rate, and a five-year survival rate of less than 5 percent.[7] The glioblastoma growth rate is 1.4 percent per day, and the volume doubling time occurs in 49.6 days, contributing to its dismal prognosis.[8] With treatment, most patients experience tumor recurrence with a diminished prognosis.[9]

The cerebral hemispheres, specifically the supratentorial major lobes, are common sites for glioblastoma.[1] Before treatment, brain tumors can alter the intracranial contents, causing unilateral headaches in 30-50 percent of cases, visual disturbances from focal neural deficits, and seizures.[10] Tumor growth produces hallucinations from seizure activity.[11] Hallucination types vary by etiology and pathological location.[10] Visual field deficits occur from tissue destruction affecting the visual pathway—supramarginal gyrus, angular gyrus, and tumors in the parietal-occipital junction.[12] Acute subjective complaints of visual disturbances in the form of complex hallucinations or visual field loss present an opportunity for early diagnosis, lesion localization, and swift intervention.

The parietal neurons contribute to sensorimotor function as an interface between perception and action.[13] The spatial perception stimuli received by parietal lobe neurons originate from receptor surfaces such as the retina.[14] The

parietal cortex contains a complex neuronal construct subject to visuospatial perception dysfunction, particularly with right parietal lobe damage.[15] Surgical removal of parietal lobe tumors is the mainstay of treatment, during which impairment of any sensorimotor functions is likely before and after the resection. The case study subject experienced postoperative sensory deficits that are well-documented in neuroscience, such as a lapse in determining the perceptual orientation of extrinsic objects in his extra personal space.[16]

CASE REPORT

A 76-year-old man presented for an urgent evaluation with complaints of a recent onset of intermittent kaleidoscope-like transient disturbances in his vision that alternated between his right and left sides for ten-minute durations. He noticed multiple episodes a day for one month. He also described seeing images of people and cars moving past him on his left side. He recounted the actions of the people he saw in his hallucinations as bending down and wearing red tee shirts. The visual images appeared with opened or closed eyes. He had no blurred vision, transient vision loss, or diplopia. He had no history of head trauma or eye injury. He complained of headaches that he attributed to neck arthritis. The head pain originated in the lateral neck radiating bilaterally to the parietal area of his head. His headaches were constant with increasing severity for two months. He admitted waking with a headache. He denied nausea or vomiting, strange smells, limb paralysis, or cognitive changes.

His medical history included psychiatric care for anxiety disorder for eleven years, with no recent psychiatric visits and no prescribed antipsychotic medications. He admitted well-controlled hypertension and hypercholesterolemia. His systemic medications included the diuretic hydrochlorothiazide (Sandoz, Germany), atenolol (Sandoz, Germany) for hypertension, and simvastatin (Zocor, Merk & Co., Rahway, NJ) for hyperlipidemia. He had no history of cancer and no known medical or environmental allergies.

His best corrected visual acuity was 20/20 in each eye. His ocular motor exams were normal. His neurological exam revealed a cranial nerve II transmission abnormality manifesting as a visual field defect. No gross abnormalities were detected in either cranial nerve I or III-XII. A dilated ocular health exam was completed and did not reveal contributory findings for his hallucinations and headache symptoms.

Optical coherence tomography (Zeiss, Dublin, CA) imaging of the macula and optic nerve was unremarkable. The automated Humphrey Visual Field 24-2 SITA-Faster test (Zeiss, Dublin, CA) revealed an incongruous left homonymous hemianopia denser inferiorly, as shown in a single visit structure-function analysis display (Figure 1).

His diagnoses included a neurological visual field defect, the suspicion of intracranial pathology with a progressive headache, intermittent visual disturbances, and complex hallucinations. The patient was educated on the risk of intracranial pathology, specifically a brain tumor, and the indication for neuroimaging.

Three days after his optometry visit, the radiology report detailed the findings of a 2.0 x 2.0 x 1.7 cm peripherally enhancing intra-axial hemorrhagic lesion within the inferior right parietal lobe with moderate surrounding white matter vasogenic edema without midline shift (Figure 2). The magnetic resonance imaging axial view showed the peripherally enhancing mass in the inferior right parietal lobe precuneus, effacing the white matter between the calcarine sulcus and parietal-occipital sulcus (Figure 3). The structural characteristics showed calcific or hemorrhagic properties denoted by the non-enhancing central darkness. The sagittal orientation of the neuroanatomy showed the mass location and tissue alteration proximal to the occipital lobe (Figure 4).

Four days after his optometry visit, he underwent a right parietal craniotomy with isocitrate dehydrogenase intracranial neurosurgical resection of a well-circumscribed isocitrate dehydrogenase wildtype glioblastoma measuring 2.8 × 1.5 × 1.2 cm concomitantly with radiation treatment. In addition, his oncology medical treatment included oral temozolomide (Merck, Sharp, Dohme, Rahway, NJ) 140 mg two hours before his radiation treatment five days a week for 12 weeks.

OPTOMETRY FOLLOW-UP

He presented three months postoperatively. His last visit with his neurosurgeon was one day prior, and he finished the first course of radiation and oral chemotherapy. He reported headache resolution and cessation of the visual hallucinations immediately following his procedure. He had no blurred or decreased central vision. He reported noticing a blind spot in his left temporal field after the surgery.

He reported fatigue and episodes of forgetfulness that he described as difficulty visualizing the location of objects in space since the procedure, a common symptom of the somatosensory dysfunction associated with parietal lobe disease. For example, he required multiple attempts to locate a wall light switch while reaching to turn it on. This phenomenon illustrated an example of a parietal lobe spatial perceptual deficit and explained his difficulty with visually guided movement coordination. Fortunately, with effort, he conducted his routine activities adequately.

His best corrected visual acuity remained 20/20 in each eye. No changes were detected in his afferent visual field testing and ocular motor testing. A healing 6 cm long surgical craniotomy incision extending anteriorly to posteriorly on the right-side parietal region was observed on a shaved area of his scalp. His anterior segment ocular health was unchanged. The dilated fundus exam showed no new pathological signs.

Follow-up optical coherence tomography studies of the optic nerve and retinal nerve fiber layer were unchanged in each eye. The postoperative automated visual field test in the single visit structure-function analysis (Figure 5) showed a persistent incongruous left homonymous hemianopia denser inferiorly respecting the vertical midline.

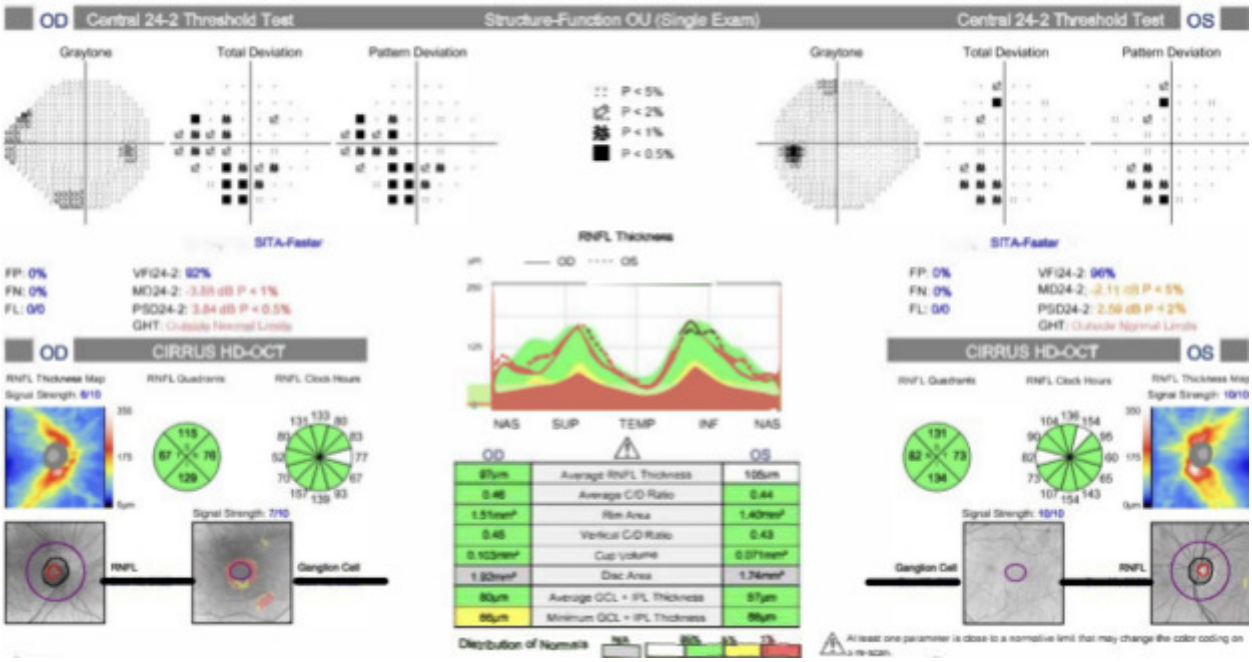

Figure 1. Preoperative Humphrey visual field 24-2 test results included in a single visit structure-function analysis correlating optic nerve and retinal nerve fiber layer analysis with perimetric defects.

The left incongruous homonymous hemianopia contralateral to the parietal lobe lesion location resulted from visual pathway damage. The optical coherence tomography nerve fiber layer analysis showed no abnormalities

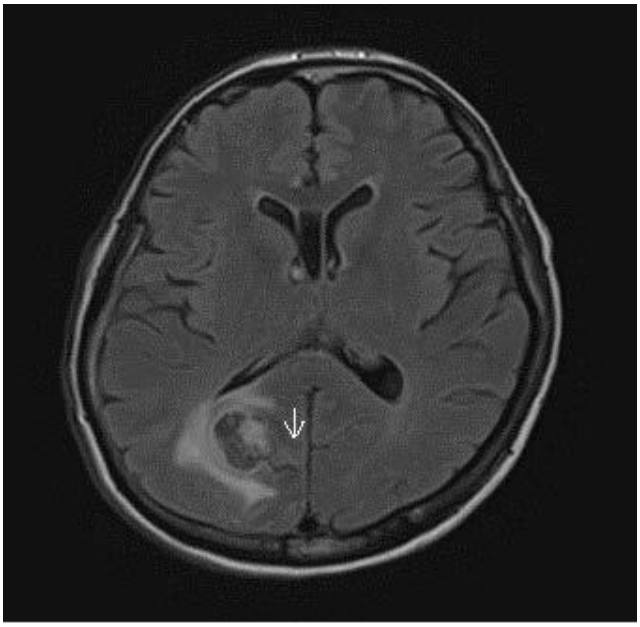

Figure 2. Preoperative magnetic resonance axial flair sequence showing the right parietal mass proximal to the posterior aspect of the splenium of the corpus callosum and the effaced parietal-occipital sulcus from glioblastoma invasion (white arrow)

He was diagnosed with an incongruous left homonymous hemianopia denser inferiorly, corresponding to a history of a right parietal lobe glioblastoma status post right craniotomy with maximum resection followed by chemoradiotherapy and adjuvant temozolomide chemotherapy. He was

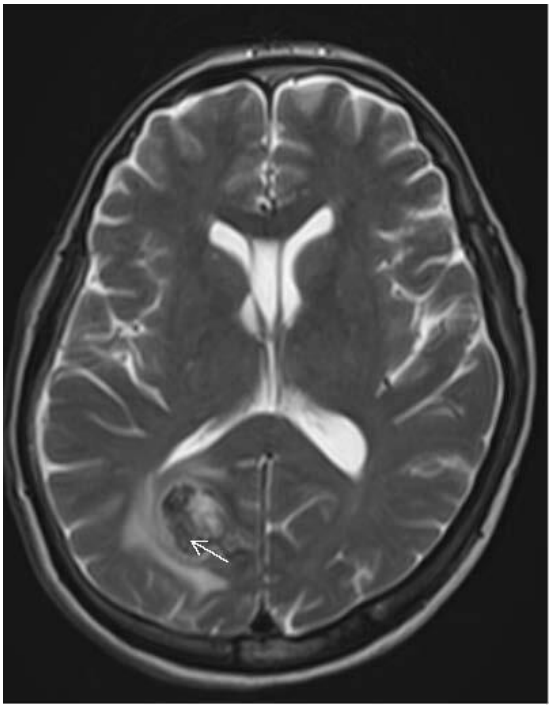

Figure 3. Preoperative magnetic resonance axial T2 imaging sequence highlighting the dark space in the right parietal lobe containing the hemorrhagic glioblastoma (white arrow) with surrounding vasogenic edema.

The lesion extended into the cuneus between the calcarine sulcus and parietal-occipital sulcus

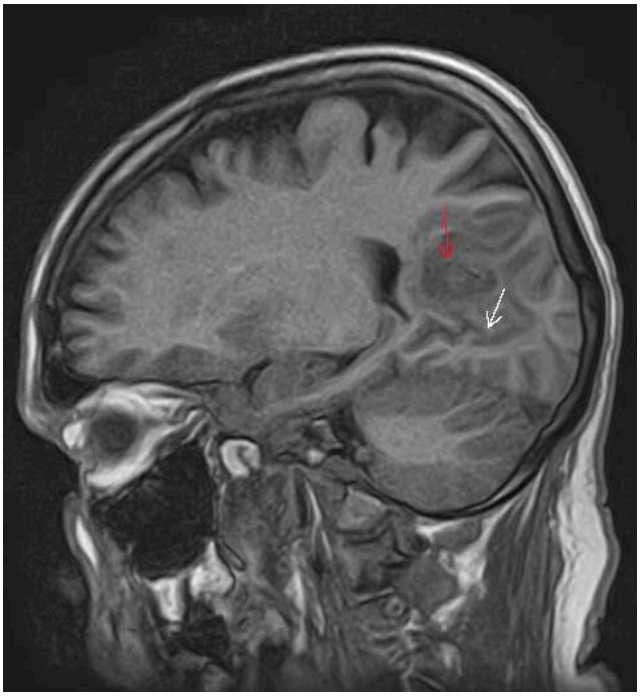

Figure 4. Preoperative magnetic resonance sagittal TI weighted 3-dimensional inversion recovery (IR) slice showing the parietal lobe mass (red arrow), calcarine sulcus (white arrow), and the lesion proximity to the occipital lobe

educated about the spatial perception symptoms he experienced due to the tumor's location. He was encouraged to log his experiences to discuss with his neurologist as he discovered the extent of his brain damage. His neurology follow-up was in one month when the second course of radiation and chemotherapy commenced.

DISCUSSION

PATHOLOGICAL CLINICAL CONSIDERATIONS

When glioblastoma induces an incongruous visual field homonymous hemianopia, the defect can be localized to the fibers of the geniculocalcarine tracts.[17] Forming the dorsal optic radiation and Meyer's loop through both parietal and temporal pathways, the geniculocalcarine tracts terminate in the visual cortex's cuneus and lingual gyrus.[16] As most clinical presentations of headaches are not subjected to neuroimaging, routine visual field testing is beneficial particularly when headache symptoms escalate to tumor suspicion. Headaches associated with glioblastoma can be severe, refractory, and accompanied by nausea and vomiting.[18] Neurological symptoms often guide the eye exam and confirm the presence of a tumor (Table 1).[19]

The onset of visual disturbances can precede tumor diagnosis. Likewise, tumor induced seizures can trigger hallucinations, the perception of objects or visual events without an external stimulus.[10] Three hallucination types include the psychophysiology pathogenesis of altered brain anatomy, the neurotransmitter-causing psychobiological, and psychodynamic hallucinations resulting from unconscious streams into consciousness.[10] Complex hallucinations can result from disturbances of the interdependent relationship between brain anatomy and chemistry or seizure activity at visual processing cortical centers.[10]

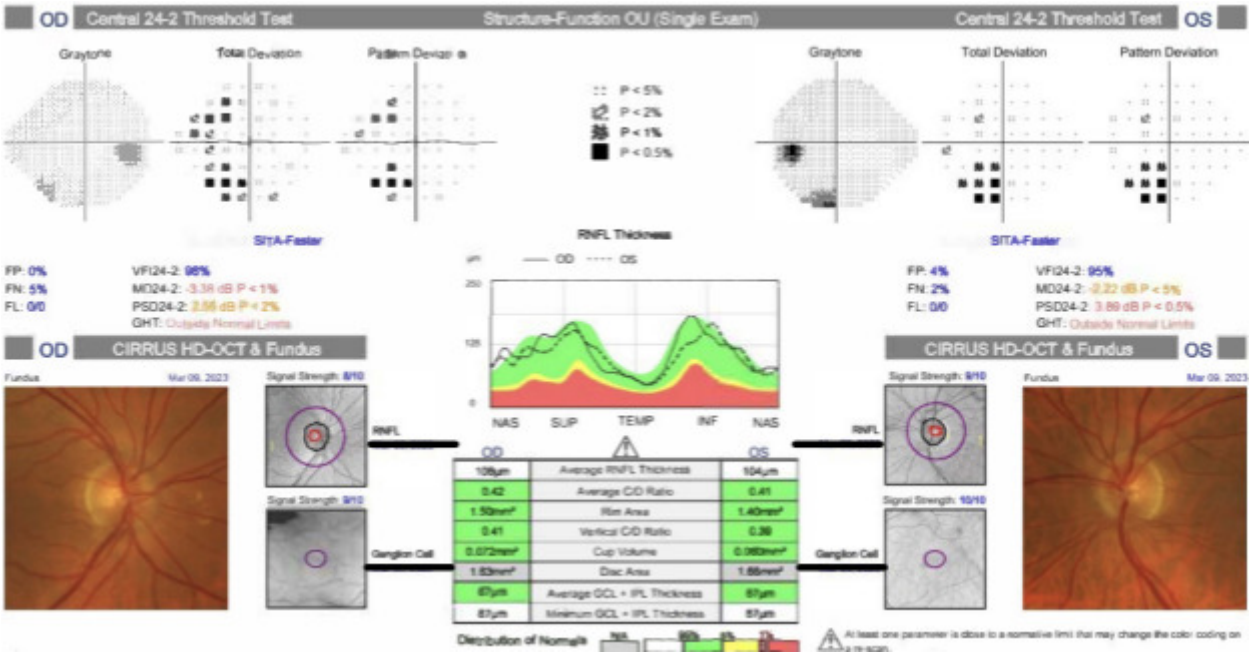

Figure 5. Postoperative Humphrey visual field 24-2 test results included in a single visit structure-function analysis correlating the optic nerve appearance and retinal nerve fiber layer analysis with the persistent perimetric defect.

The left incongruous homonymous hemianopia contralateral to the parietal lobe lesion location resulted from visual pathway damage. The optical coherence tomography nerve fiber layer analysis showed no abnormalities

Neurological Exam	Neurological Signs and Symptoms
Pupils	Rare relative afferent pupillary defect, anisocoria[19]
Optic Nerve	Decreased visual acuity, dyschromatopsia, optic disc pallor, papilledema[1,19]
Visual Field	Unilateral visual field defects, heteronymous hemianopia, homonymous hemianopia[17]
Headache	Severe calcitrant progressive headache, pulsating headache[1,19]
Visual Processing	Abnormal visual-spatial awareness, spatial neglect, sensory-motor dysfunction, visual dyspraxia[19]

Table 1. List of potential ocular and neurological signs and symptoms of glioblastoma

Moreover, hallucinations involving vivid scenes, such as people carrying out tasks, are thought to be related to tumor activity.[5]

Magnetic resonance imaging is the most important diagnostic tool for glioblastoma detection.[20] Glioblastomas showing substantial gadolinium contrast enhancement with central necrosis signal a higher-grade tumor.[11] The magnetic resonance imaging spectroscopy modality is helpful in diagnosing challenging lesions.[19] It provides a noninvasive analysis quantifying the chemical composition of metabolites in a tumor tissue sampling.[19]

Glioblastoma alterations such as the isocitrate dehydrogenase wildtype mutation are detected by immunohistochemistry, and notably, identifying intratumor genetic mutations can predict prognosis and treatment response.[21] Immunohistochemistry enables pathologists to determine the exact type and subtype of cancers by looking for unique markers within cancer cells.[22] It combines anatomical, immunological, and biochemical imaging techniques to visualize and document intracellular components using antibodies to bind to targeted antigens in situ.[21]

The aggressive nature of glioblastomas makes it impossible for neurosurgeons to cure the tumor entirely.[1] The World Health Organization established a tumor proliferative index that increases with tumor grade.[3] Thus, grade IV glioblastoma aggressively invades surrounding tissues.[3] Glioblastoma treatment involves maximum tumor resection, radiotherapy, and temozolomide.[5] Surgery is limited by the protocol to preserve adjacent brain tissue required for normal neurological function.[3] In glioblastoma oncology treatment, temozolomide is an alkylating prodrug used to cross the blood-brain barrier and disrupt cell DNA structure by delivering a methyl group to purine bases of DNA (O6-guanine; N7-guanine and N3-adenine).[23] Temozolomide kills normal and cancerous cells yet is more harmful to rapidly dividing tumor cells.[22] A newer modality in noninvasive therapy, tumor treating fields (TTFields), uses alternating electrical fields of intermediate frequencies to pulse through the scalp, disrupt tumor cell division, or cause tumor cell death.[24] The avoidance of radiotherapy eliminates the risk of radiation necrosis and neuroinflammation linked to brain damage and cognitive impairment.[25]

AFFECT OF GLIOBLASTOMA ON THE PARIETAL LOBE

The parietal neurons contribute to sensory spatial perception.[13] Neuronal activity in the parietal lobe integrates multiple streams of sensory data to process the proximal relationship of different body parts to each other, orient the body's relationship to other objects in space, and orient extrinsic objects to each other in the extra personal space.[15] The parietal region also analyzes space using sensory modalities, specifies spatial targets for the motor system, generates attention, and analyzes visual motion.[14]

Anatomically, the parietal lobe is divided into the postcentral gyrus, the supramarginal gyrus, the angular gyrus, and the superior parietal lobule on the outer hemisphere surface.[26] The supramarginal and angular gyri comprise heteromodal cortex neurons receiving convergent inputs from other cortex regions dedicated to processing sensory modalities.[15] Specifically, the sensory data from visual system projections such as the dorsal visuofugal pathway, in which a combination of retinotopic and visuomotor information results in the computation of events within the extra personal space.[14] The sensory deficits experienced after tumor resection can be localized to exact locations within the parietal lobe. Neglect, or the propensity to ignore objects in the half of space opposite the side of the lesion, is a behavioral consequence observed after the development of parietal cortex lesions.[13]

Neurons in the intraparietal sulcus respond to visual stimuli and memory-guided eye movements.[25] With difficulty locating and turning on a light switch, the subject in this case study appeared to experience deficits in the parieto-occipital sulcus extrastriate areas V6 and V6A for functional visuomotor coordination.[27] In addition to describing a deficit of spatially directed reaching arm movements, the subject had an impaired response to visual stimuli and memory-guided eye movements, signaling intraparietal sulcus damage.[28]

CONCLUSION

Glioblastomas are aggressive tumors that cause symptoms early in their development, and with prompt identification, survival time can increase. Surgery was performed four days after the optometry visit, and the patient suffered low postoperative morbidity. Although elderly, he responded well to the adjuvant chemotherapy. The tumor resection impacted his sensory and motor function; nevertheless, the rapid neurology response enabled him to survive with the best possible quality of life. No identifiable health information was included in this case report.

TAKE HOME POINTS

- Glioblastoma is mitotically active with a growth rate of 1.4 percent per day and a volume doubling time of 49.6 days.
- Subjective symptoms of visual disturbances in the form of hallucinations or visual field loss prompt an early diagnosis and lesion localization.

- Parietal lobe glioblastoma surgical resection contributes to neuronal disruption, impairing neurosensory function.

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CLINICAL INSIGHTS IN EYECARE
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Abbott K, Engle M, McCourt E. Case Report: Neurotrophic Ulcer Secondary to a Hypoplastic Trigeminal Nerve in a Three-Year-Old Boy. *Clinical Insights in Eyecare*. 2024;2(2).

Case Reports

Case Report: Neurotrophic Ulcer Secondary to a Hypoplastic Trigeminal Nerve in a Three-Year-Old Boy

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Keywords: neurotrophic keratitis, trigeminal nerve, cenegermin, human nerve growth factor, corneal neurotization surgery, neurotrophic ulcer

Clinical Insights in Eyecare

Vol. 2, Issue 2, 2024

Introduction

We present a challenging case of a boy aged 3 years with a refractory neurotrophic ulcer secondary to congenital trigeminal anesthesia treated with recombinant human nerve growth factor and corneal neurotization surgery.

Case Report

A boy aged 3 years presented with a nonresolving neurotrophic corneal ulcer after unsuccessful treatment consisting of topical antibiotics, steroids, and lubricating eye drops. Prior magnetic resonance imaging revealed a congenital hypoplastic trigeminal nerve. After no improvement with amniotic membrane transplantation and tarsorrhaphy, and minimal improvement with allogenic serum eye drops, recombinant human nerve growth factor resolved the neurotrophic ulcer in 1 week. Because of repeated corneal injury and high risk of progression, the boy underwent corneal neurotization surgery, which was successful.

Conclusion

This case adds to the growing body of literature supporting the use of recombinant human nerve growth factor for acute neurotrophic ulcers and neurotization in the long-term treatment of congenital neurotrophic keratitis.

INTRODUCTION

The cornea is innervated by the ophthalmic division of the trigeminal nerve.[1] This innervation is responsible for sensation, epithelial wound healing, tear production, blink reflex, and trophic functions.[1] Neurotrophic keratitis describes disruption of this innervation and reduced corneal sensation, which can be categorized by the Mackie classification system as mild punctate keratopathy (stage 1), a persistent corneal epithelial defect (stage 2), corneal ulceration (stage 3), or even corneal perforation.[2,3] Trigeminal nerve impairment may be acquired or congenital. Complete loss of trigeminal innervation from birth may be referred to as congenital trigeminal anesthesia, which is often associated with severe vision loss.[2,4] Often it manifests as conjunctival redness, nonhealing or recurrent corneal epithelial defects, and corneal scarring.[5] The most common causes of congenital trigeminal anesthesia include posterior fossa tumors, cerebellar hypoplasia, head trauma, Goldenhar syndrome, familial dysautonomia, and that of idiopathic origin.[5]

We present a case of a neurotrophic ulcer in a child with a congenital hypoplastic trigeminal nerve and concurrent septo-optic dysplasia with pituitary and gray matter abnormalities. This case report details treatment of this neurotrophic ulcer using the combination of amniotic membrane transplantation, tarsorrhaphy, allogenic serum eye drops, recombinant human nerve growth factor, and corneal neurotization surgery. No identifiable health information was included in this case report.

CASE REPORT

A boy aged 3 years with septo-optic dysplasia and developmental delay presented for a bilateral myringotomy and pressure-equalizing tube placement surgery, along with an ophthalmology consultation under anesthesia, for a nonhealing corneal ulcer of the right eye despite treatment with topical antibiotics and corticosteroids during the prior several months by an outside ophthalmologist. Examination revealed 3+ injection of the conjunctiva, a 5 mm by 5 mm corneal ulcer (Figure 1) with an epithelial defect and central corneal opacification. He was treated with a cryopreserved amniotic membrane (Prokera: Miami, Florida: BioTissue) and a temporary suture tarsorrhaphy. The ulcer was suspected to be neurotrophic given the chronicity and lack of pain.

On day 31, the tarsorrhaphy and the amniotic membrane were removed. Examination demonstrated no improvement in the corneal defect size, no infiltrate, and 5% to 10%

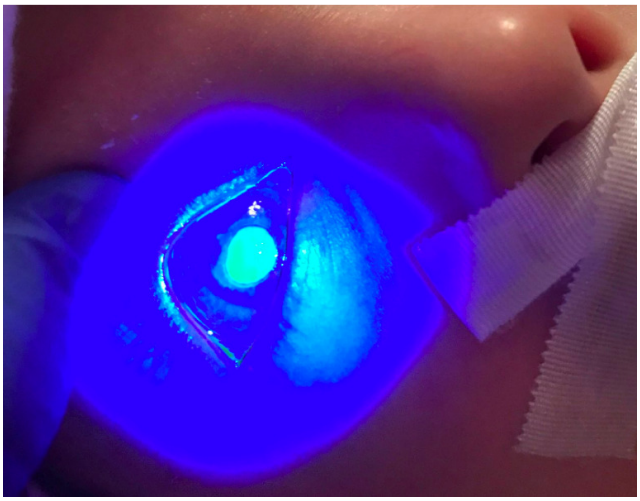

Figure 1. Right eye with sodium fluorescein demonstrating sizable corneal epithelial defect.

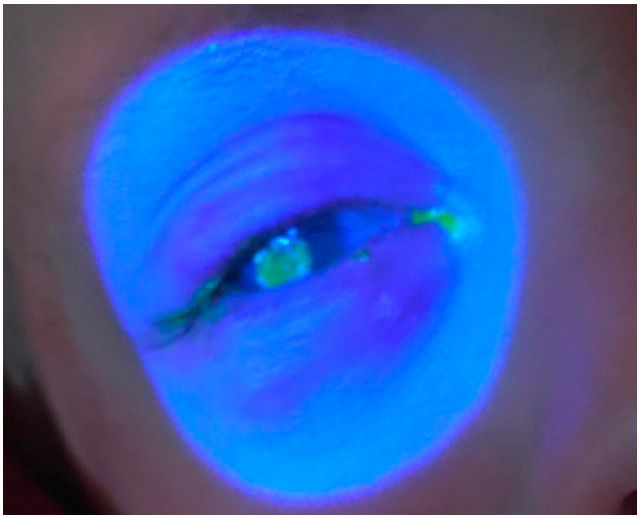

Figure 2. Right eye with sodium fluorescein demonstrating sizable corneal epithelial defect after amniotic membrane transplantation.

corneal thinning (Figure 2). Visual acuities were difficult to assess given age and developmental delay and were reported as "fix and follow" in each eye individually at each visit. A bandage contact lens was placed on the right eye and the patient was started on moxifloxacin 4 times per day, and erythromycin ophthalmic ointment as needed for lubrication. The child was also prescribed recombinant human nerve growth factor (Oxervate, 0.002% cenegermin-bkbj ophthalmic solution: Milano, Italy: Dompe farmaceutici) to use 6 times per day in the right eye on medication arrival. Extraocular muscle movements and confrontation visual fields were normal. The left pupil was round and responsive to light, whereas the right pupil was unable to be assessed because of corneal scarring.

Five days later, the corneal defect of the right eye was slightly improved. The recombinant human nerve growth factor had not arrived. Allogenic serum eye drops, from parental serum, were prescribed to be used 4 times per day,

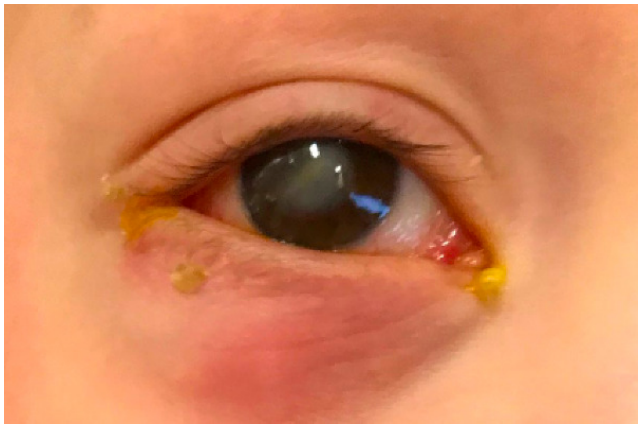

Figure 3. Right eye 2 weeks post–recombinant human nerve growth factor course demonstrating quiet ocular surface and corneal scarring.

and the bandage contact lens was replaced as it had fallen out the day after being inserted. The patient was to continue using moxifloxacin 4 times per day and erythromycin at nap and at night and to patch the right eye when able. Preservative-free artificial tears were also recommended to be used every 1 or 2 hours in the right eye.

On day 50, the bandage contact lens was in place and the patient had a smaller epithelial defect measuring 4mmx3mm. The patient had not started the allogenic serum eye drops nor the recombinant human nerve growth factor eyedrops. At this visit, the allogenic serum eye drops had just arrived, and the parents were instructed to begin instilling them 4 times per day. The bandage contact lens was also replaced.

On day 59, the corneal epithelial defect remained stable with no infiltrate. However, inferior neovascularization of the cornea was forming. The recombinant human nerve growth factor had arrived, and parents were instructed to instill 6 times per day along with allogenic serum eye drops 4 times per day and moxifloxacin 4 times per day. The bandage contact lens was removed.

On day 66, the corneal epithelial defect was completely resolved and the inferior neovascularization was receding. The plan was to continue recombinant human nerve growth factor 6 times per day for the next 7 weeks and continue allogenic serum eye drops 4 times per day indefinitely. The moxifloxacin was discontinued at this visit.

At day 136, the patient had been off recombinant human nerve growth factor for roughly 2 weeks. The cornea was still epithelialized, and a central corneal opacity remained (Figure 3). The plan was to continue allogenic serum eye drops 4 times per day indefinitely.

Unfortunately, in the next 2 years the patient experienced repeated self-inflicted corneal abrasions, which required daily bandage contact lens wear and patching of the right eye when possible. Because of these repeated injuries and risk of further corneal complications, it was decided that the best option was corneal neurotization surgery of the right trigeminal nerve. On day 954, he underwent corneal neurotization using the right sural nerve and contralateral superior orbital nerve. At his most recent follow-

up on day 1401, his right cornea was free of epitheliopathy with a treatment consisting only of preservative-free artificial tears as needed. There was also an improvement of the corneal scarring. Clinicians and guardians of the child had no concerns regarding adherence throughout the treatment course.

DISCUSSION

Congenital neurotrophic keratitis or congenital trigeminal anesthesia generally presents during infancy or within the first few years of life as eye redness, nonhealing corneal epitheliopathy or defects, and corneal scarring. In cases of discordance in which a child is experiencing minimal symptoms with significant corneal findings, congenital trigeminal anesthesia should be included in the differential diagnosis list. This is especially true if there is any accompanying brain malformation, cranial nerve palsies, facial dysmorphism, developmental delay, or nonhealing skin lesions along the trigeminal nerve distribution. Congenital trigeminal anesthesia can be subdivided into 3 types based on trigeminal nerve embryology.[6]

Rosenberg Classification of Congenital Trigeminal Anesthesia[6]

- Type I: isolated
- Type II: ectodermal or mesodermal maldevelopment
- Type III: focal brainstem pathology potentially from a vascular prenatal event without evidence of systemic developmental abnormalities

Although the sensory portion of the trigeminal nerve arises from the neural crest, the motor portion develops from the neural tube.[7] The neural crest is responsible for mesodermal and some ectodermal development, which explains why congenital trigeminal anesthesia may be associated with skull, spine, or ear malformations.[8] In this classification system, type I is considered an isolated event and confined to the cornea only, type II is related to mesodermal and ectodermal embryonic development, and type III is related to focal brainstem malformations secondary to prenatal injury, likely vascular in nature. In type I, the key classification is the absence of other neurological or mesoectodermal congenital abnormalities. This type typically only involves the ophthalmic division of the trigeminal nerve and etiology is thought to be due to primary hypoplasia of the trigeminal nuclei/hindbrain. Bilateral cases are more common than unilateral. Type II is associated with mesodermal and/or ectodermal developmental disorders such as Goldenhar syndrome or oculoauriculovertebral spectrum, Moebius syndrome, VACTERL association (vertebral, anal, cardiovascular, tracheoesophageal, renal, and limb defects), MURCS association (Müllerian duct aplasia–renal agenesis–cervicothoracic somite dysplasia), Riley-Day syndrome (familial dysautonomia), and congenital insensitivity to pain. This type can be unilateral, more commonly seen in patients with Goldenhar syndrome, or bilateral, more common in patients with non-Goldenhar syndromes. In type III, there is a prenatal injury, likely vascular in nature, that causes focal brainstem abnormalities with no evidence of any systemic developmental abnormalities.[4] An example of type III congenital trigeminal anesthesia would be a patient presenting with unilateral corneal anesthesia with ipsilateral sixth and seventh nerve palsies without systemic abnormalities caused from a prenatal ischemic insult.

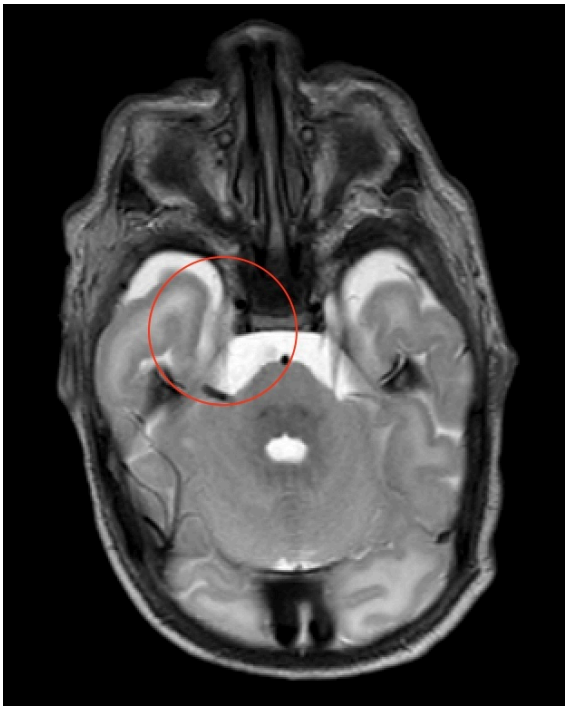

Figure 4. Hypoplastic right trigeminal nerve at 1 month of age.

Despite no diagnosed genetic syndrome, we believe our patient has type II congenital trigeminal anesthesia given his significant medical history of septo-optic dysplasia with associated growth hormone deficiency and central hypothyroidism, global developmental delays with hypotonia, autism spectrum disorder, and sensorineural hearing loss. Magnetic resonance imaging of the brain and orbits performed when the child was aged 1 month revealed posterior pituitary ectopia, subependymal gray matter heterotopia, and left occipital subcortical gray matter heterotopia with overlying polymicrogyria, multiple cranial nerve abnormalities including bilateral optic nerve hypoplasia, a hypoplastic right trigeminal nerve, and small cochlear nerves (Figure 4). Repeat neuroimaging was performed at 4 years and 2 months of age (Figure 5) demonstrating stability of the septo-optic dysplasia and hypoplastic right trigeminal nerve.

Unfortunately, at our initial examination, our patient already had advanced corneal scarring and a neurotrophic ulcer with corneal thinning consistent with stage 3 neurotrophic keratitis. Early identification and treatment of congenital neurotrophic keratitis is essential as this may lead to fewer complications and better visual outcomes. However, even with early intervention, permanent vision loss is still common. Microbial keratitis is a concern in pediatric cases of corneal anesthesia, with approximately 45% developing an infection and 35% having an infection at presentation.[5] Corneal scarring occurs in 73% of children with

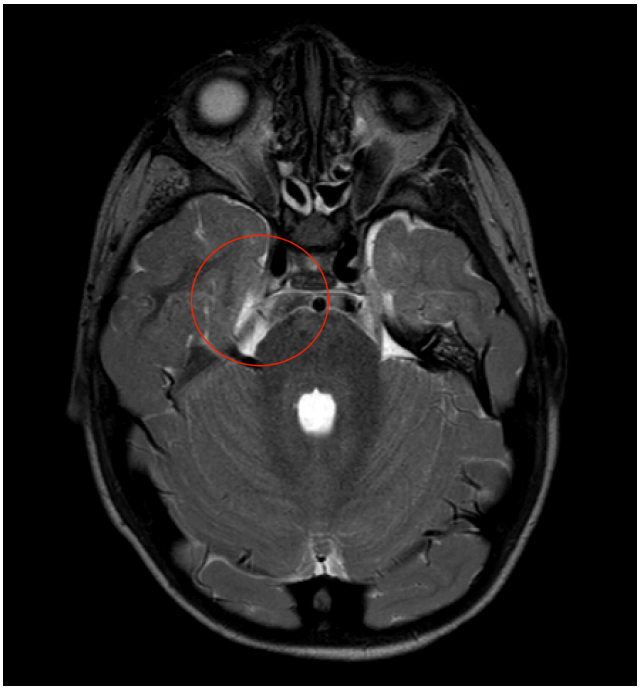

Figure 5. Hypoplastic right trigeminal nerve at 4 years and 2 months of age.

corneal anesthesia.[5] In a 2-center retrospective cohort by Lambley with 33 eyes from 26 children with corneal anesthesia, only 15% had a final visual acuity of 20/40 or better, 30% worse than 20/200, and the rest between 20/40 and 20/200.[5] Visual prognosis was worse in patients with a concomitant facial nerve palsy.[5] We were unable to measure quantitative visual acuity in our patient because of age and developmental delay.

Treatment options for neurotrophic keratitis or congenital trigeminal anesthesia include lubricating eye drops, bandage contact lens wear, amniotic membrane transplantation, allogenic serum eye drops, recombinant human nerve growth factor, topical insulin, substance P, insulin-like growth factor, tarsorrhaphy, scleral contact lenses, and corneal neurotization surgery.[9] The aggressiveness of the treatment is primarily dependent on the stage of the neurotrophic keratitis. In our patient, there was no improvement in corneal epithelization with amniotic membrane transplantation combined with tarsorrhaphy and the corneal epithelium only marginally healed using allogenic serum eye drops despite the epitheliotrophic growth factors present in such drops. Although tarsorrhaphy, bandage contact lens wear, and topical antibiotics prevented microbial keratitis, this reduced corneal exposure also did not resolve the neurotrophic ulcer. Although topical insulin has shown promising effects in the treatment of neurotrophic keratitis, it was not considered in this case as there was minimal research supporting its use at the time and because of its limited availability.[10] The recalcitrant neurotrophic ulcer healed in 1 week or less with recombinant human nerve growth factor presumably because of the higher concentration of nerve growth factor present in recombinant human nerve growth factor as compared with allogenic serum eye drops. Early evidence demonstrates the effectiveness of recombinant human nerve growth factor in the treatment of pediatric neurotrophic keratitis.[11,12] Corneal neurotization is a surgery that uses a local nerve or graft to reinnervate an anesthetic or hypoesthesic cornea.[13] When the sural (afferent) nerve is used, this is considered an indirect interposition technique rather than a direct transfer procedure (contralateral vs ipsilateral). Despite the problem originating upstream in the trigeminal ganglion, reinnervation to the downstream corneal nerves is possible via retrograde neuronal effects from the rerouted donor nerve.[14] This new innervation of the corneal nerves delivers protection and viability to the ocular surface. Preliminary evidence demonstrates that neurotization surgery yields clinically significant improvements in corneal sensation, visual acuity, and ocular surface integrity.[13] because of repeated corneal injury, our patient eventually underwent corneal neurotization surgery, which was successful. Eyes with corneal anesthesia are particularly susceptible to traumatic epithelial injury because of reduced sensation as well as reduced epitheliotrophic factors secreted by the corneal nerves.[10] Such epithelial damage predisposes these corneas to infection, ulceration, scarring, and perforation, which increase the risk of deprivation and refractive amblyopia in children.

Patients with congenital trigeminal anesthesia should be screened for brain malformations, mesodermal and ectodermal abnormalities, and skeletal deformities. Our patient had a brain magnetic resonance imaging prior to our initial examination and was diagnosed with septo-optic dysplasia and a hypoplastic right trigeminal nerve among other brain malformations. Parents or guardians should be educated on the risk of injury to the face and eye due to reduced or absent trigeminal sensation. Prior to corneal neurotization surgery, we attempted to mitigate this risk using daily bandage contact lens wear and patching the eye but were ultimately unsuccessful in preventing corneal injury.

CONCLUSION

Although pediatric cases of neurotrophic keratitis are relatively rare, they tend to be severe and recalcitrant. This case used amniotic membrane transplantation, topical antibiotics, bandage contact lenses, allogenic serum eye drops, preservative-free artificial tears, recombinant human nerve growth factor, and finally, corneal neurotization surgery. This case adds to the growing body of evidence for the effectiveness of recombinant human nerve growth factor in healing pediatric neurotrophic ulcers and corneal neurotization surgery for restoration of trigeminal nerve function. No identifiable health information was included in this case report.

TAKE HOME POINTS

- This is a challenging case of a 3-year-old patient with a refractory neurotrophic corneal ulcer secondary to a rare congenital trigeminal anesthesia.
- The use of recombinant human nerve growth factor resulted in the resolution of the neurotrophic ulcer in

just one week, highlighting the effectiveness of this treatment approach.

- Corneal neurotization surgery was successful in restoring corneal nerve function, suggesting its potential as a long-term treatment option for congenital neurotrophic keratitis.

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CLINICAL INSIGHTS IN EYECARE
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Conto JE, Hogan JN, Lim SJ. Case Report of Corneal Ulceration Associated With Dupilumab. *Clinical Insights in Eyecare*. 2024;2(2).

Case Reports

Case Report of Corneal Ulceration Associated With Dupilumab

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Keywords: dupilumab, atopic dermatitis, atopic keratoconjunctivitis, corneal ulceration

Clinical Insights in Eyecare

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Introduction

Dupilumab (DUPIXENT, Regeneron & Sanofi, USA) increases the risk for ocular surface complications in predisposed patients. Although keratoconjunctivitis is the most reported complication, corneal ulceration is rare. This is a case report of corneal ulceration in a patient with dupilumab-associated ocular surface disease. The current understanding of the dupilumab-associated ocular surface disorder and management will be discussed.

Case Report

A 21-year-old multiracial man presented with exacerbation of atopic keratoconjunctivitis that coincided with the start of dupilumab for the treatment of atopic dermatitis. Despite discontinuation of dupilumab, and aggressive management with topical and oral anti-inflammatory therapy, a corneal ulcer developed following dupilumab treatment.

Conclusion

This case highlights the challenges in managing atopic keratoconjunctivitis and the potential ocular side effects of dupilumab treatment in atopic dermatitis. Based on current literature, atopic keratoconjunctivitis and other ocular surface disorders are likely underdiagnosed and paradoxically exacerbated by dupilumab in the treatment of atopic dermatitis. Although reports of corneal ulceration in patients using dupilumab are limited, it is unclear if the pathogenesis represents a causative association or an exacerbation from the atopic disease itself. Therefore, patients with atopic dermatitis should be carefully monitored for any eye-related symptoms and, if they occur, have an ophthalmic evaluation. In most cases of atopic keratoconjunctivitis and dupilumab-associated ocular surface disease, continuation of dupilumab is possible.

Atopic dermatitis is a chronic, pruritic, eczematous disease that frequently starts in childhood and can continue throughout life with periods of remission and flaring. It develops because of a complex interrelationship of environmental, immunological, genetic, and pharmacological factors. Exacerbations of atopic dermatitis can occur with infections, psychological stress, climate/seasonal changes, allergens, and irritants. This presents as inflammation of the skin involving hypersensitivity, immunoglobulin E sensitization, and T-helper cell 2 activation. This results in severe pruritus and xerosis.[1,2] Atopic dermatitis mostly affects children but does occur in 5% of adults.[3-5] Atopic keratoconjunctivitis, an ocular manifestation of atopic dermatitis, is characterized by severe ocular pruritus and eyelid dermatitis.[6] Atopic keratoconjunctivitis involves both types 1 and 4 hypersensitivity reactions, causing inflammation of the periocular skin, conjunctiva, and cornea.[6] Conjunctival scarring, limbal stem cell deficiency, and corneal ulceration are severe complications that may lead to vision loss.[6,7] To improve the quality of life in patients experiencing atopic dermatitis, systemic immunosuppression is often necessary. Dupilumab (DUPIXENT, Regeneron & Sanofi, USA) was the first biologic that was approved for the treatment of atopic dermatitis in 2017. However, this highly effective treatment is associated with an increase incidence of conjunctivitis, blepharitis, keratitis, and eye pruritis, which present similarly to atopic keratoconjunctivitis. These side effects are known as dupilumab-associated ocular surface disease. Although there are ocular surface complications associated with atopic disease, corneal ulceration has rarely reported to be directly associated with the use of dupilumab.[3,7-11] However, the management and treatment is similar between atopic keratoconjunctivitis and dupilumab-associated ocular surface disease. No identifiable health information was included in this case report.

CASE REPORT

Dermatology referred a 21-year-old multiracial man for ocular inflammation. He had a long-term history of atopic eyelid dermatitis with lower-lid ectropion. He reported no surgical eye procedures. The patient had noted increased

redness, injection, and foreign body sensation in both eyes for the past 3 months.

Medical history was significant for atopic dermatitis since childhood, hyperimmunoglobulin E syndrome, and inflammatory bowel disease. Systemic medications included vedolizumab (ENTYVIO, Takeda Pharmaceuticals, USA) for 2 years and topical tacrolimus 0.03% for skin eruptions. He experienced failed treatment with other therapies, including infliximab, certolizumab, and adalimumab. Current ocular medications included 0.3% tobramycin/0.1% dexamethasone ointment applied to the eyelids twice a day where the skin eruptions persisted. He reported using fluorometholone 0.1% drops in the past, which were prescribed by his primary care physician.

The examination revealed uncorrected visual acuities of 20/20 in the right eye and 20/25 in the left eye. The pupils were round and reactive to both light and near targets. There was no afferent pupillary defect noted. Extraocular motilities were full, and confrontation visual fields did not demonstrate any central or peripheral depressions or defects in either eye.

The external examination demonstrated patchy, eruptive lesions of the forehead and periorbital dermis, both eyes. Biomicroscopic examination showed thickened inferior eyelids with excoriation. Mild scurfs were present. There was 1+ injection of the bulbar conjunctiva and noted 1+ giant papillae on upper-lid eversion of the palpebral conjunctiva, both eyes. Scant mucoid discharge was seen in the fornixes. The corneal surface was normal in appearance, without significant punctate epithelial erosions in both eyes. The anterior chambers did not demonstrate cells or an inflammatory process in either eye. The crystalline lens did not show any cataract formation in either eye. Tonometry was 16 mm Hg in the right eye and 15 mm Hg in the left eye.

The vitreous bodies were intact. The optic disc had 0.25/0.25 cupping with symmetrical neuroretinal rim tissue in both eyes. The maculae were normal, and the peripheral retina tissue did not demonstrate any defects in either eye.

The tentative diagnoses at this time were atopic blepharoconjunctivitis and periocular dermatitis. Management included discontinuing the 0.3% tobramycin/0.1% dexamethasone ointment and replacing it with tacrolimus 0.03% ointment twice a day for both eyes. Preservative-free artificial tears were to be used, as well as humidification of his environment. Use of olopatadine 0.7% once a day for both eyes was also recommended rather than a topical corticosteroid since it was felt a mast-cell stabilizing was thought to more useful for long-term maintenance. The patient was scheduled to come back in 6 months for a comprehensive examination.

Two months after the consultation, the patient called and said that he was in “excruciating” pain. He reported that he was using more than eight vials of preservative-free artificial tears a day with no relief. He had self-discontinued the tacrolimus ointment since the skin lesions had improved. Of significance, he had begun dupilumab treatment for his atopic dermatitis 6 weeks prior to his phone call. He received his second dose 3 days prior to his symptoms increasing.

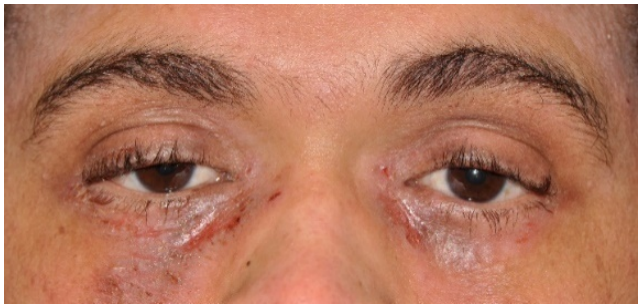

Figure 1. Facial photograph of excoriated periocular skin.

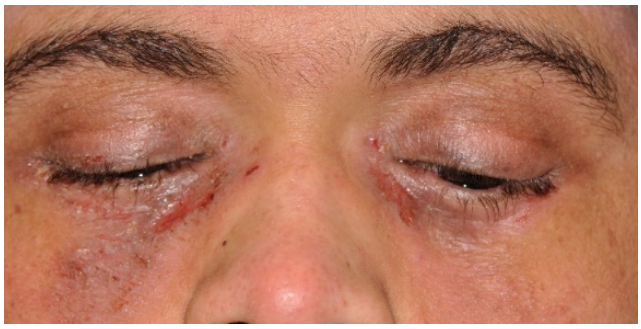

Figure 2. Facial photograph of left lagophthalmos.

Pertinent examination findings showed 2+ scaling and eruptions of the skin on the inferior periorbital region of both sides (Figure 1). Thickening and ptosis of the upper lids was evident. There was mild ectropion of the lower eyelids, both eyes, and lagophthalmos with inferior exposure of the ocular surface, left eye (Figure 2). Biomicroscopy demonstrated 2+ diffuse conjunctival bulbar injection without ciliary flush, both eyes. On upper lid eversion, 3+ giant papillae were evident (Figure 3). There was 2+ inferior corneal punctate erosions. The anterior chamber was quiet.

The history and signs indicated a tentative diagnosis of dupilumab-associated ocular surface disease. The patient was placed on prednisolone acetate 1% 4 times a day; olopatadine 0.7% twice a day, both eyes; preservative-free artificial tear drops every 4 hours, and nighttime ointment. He was instructed to restart the tacrolimus 0.03% ointment twice a day to the facial eruptions. A discussion with his dermatologist resulted with the discontinuation of further dupilumab injections. He was scheduled for a 1-week follow-up.

The patient did not return for his scheduled follow-up visit and presented to urgent care 3 weeks after his last examination, with the complaint of blurred vision, pain, and eye redness in the right eye for several days. He did not comply with treatment recommendations and self-discontinued with his topical medications except for artificial tears. He had not received another dupilumab injection. The pain was rated at 10 out of 10. He was diagnosed with allergic conjunctivitis and given olopatadine 0.1% drops 4

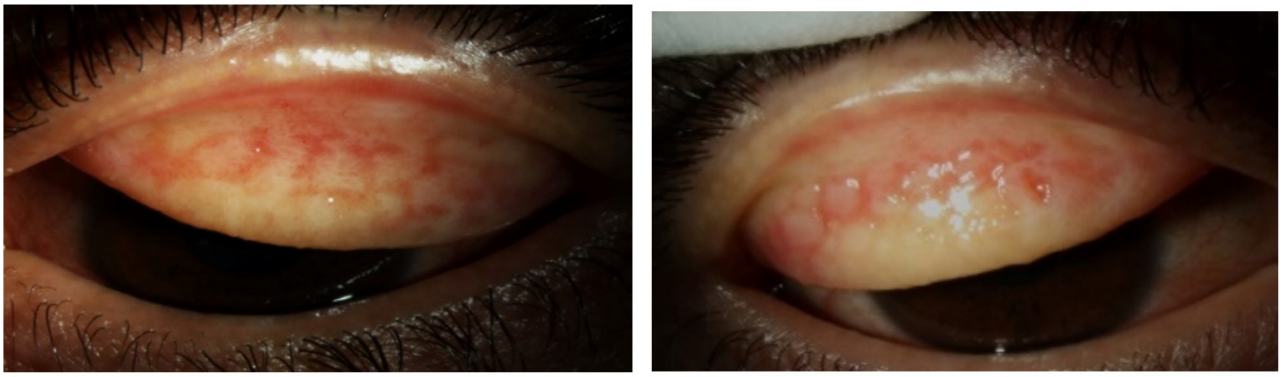

Figure 3. Slit lamp photograph of giant papillae on upper palpebral conjunctiva.

times a day, both eyes, along with use of preservative-free artificial tears. Urgent care also gave oral prednisone for the eczema. He also tried cool compresses, oral loratadine, and fluticasone propionate nasal spray without relief. He was scheduled to be seen in the vision services department the next day.

On ophthalmic examination the next day, uncorrected visual acuity was 20/80 right eye and 20/40 left eye. There was moderate photophobia present. The eyelid dermis was stable without new eruptions or erythema. Biomicroscopy demonstrated increased chemosis and injection of the bulbar conjunctiva right eye greater than the left eye. The right cornea showed a large round peripheral defect 3 mm in size with several nodular infiltrates centrally and an immune ring about 6 mm (Figure 4). There was diffuse 3+ staining sodium fluorescein of the defect. There was no mucous discharge. The anterior chamber showed a mild inflammatory reaction without hypopyon. Multiple ESwab (Copan Diagnostics) cultures of the corneal surface, the upper and lower palpebral conjunctiva, and surrounding lid margins were performed. A corneal scaping was also performed. The samples were sent to the hospital laboratory for bacterial, viral, and fungal analysis. A real-time polymerase chain reaction assay was also ordered. The left conjunctiva and cornea were unchanged from previous examination. Since the symptoms and appearance were suggestive of infectious keratitis, the patient was treated with moxifloxacin 0.5% ophthalmic solution every 4 hours and fortified tobramycin 14 mg/mL drops every 4 hours in alternating fashion until the results of the cultures were known. The patient also was given cyclopentolate 1% twice a day in the right eye. The patient was instructed to continue to use preservative-free artificial tears in both eyes. He was to resume use of the tacrolimus 0.03% ointment to the periocular lid tissue, right eye.

The patient was seen 2 days later and reported mild improvement in comfort and vision. He reported compliance with the moxifloxacin, tobramycin, and cyclopentolate. Examination showed improved uncorrected visual acuity to 20/40 in the right eye and 20/30 in the left eye. Slit lamp revealed a smaller defect about 2 mm in size. The immune ring and infiltrates were still present. Conjunctival injection was reduced, and the anterior chamber reaction was limited to trace cells. The bacterial and fungal cultures showed no growth at 24 and 48 hours. The polymerase chain reaction assay was pending.

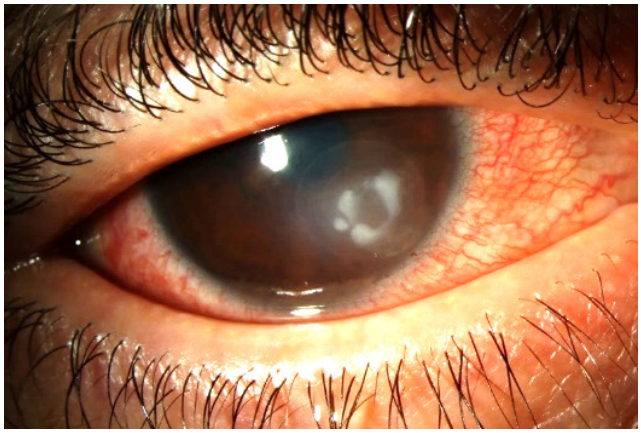

Figure 4. Slit lamp photograph of corneal ulcer with immune ring.

Since there was no pathogen growth and the defect was smaller, tobramycin was replaced with 0.3% tobramycin/0.1% dexamethasone ophthalmic suspension every 4 hours. The moxifloxacin was reduced to every 4 hours again in alternating fashion with the 0.3% tobramycin/0.1% dexamethasone. The cyclopentolate was discontinued.

Five days later, the patient reported substantially better comfort and improved vision in the right eye. He continued to use the moxifloxacin and tobramycin/dexamethasone as instructed.

The corneal epithelial defect was only 0.5 mm in size, and the infiltrates appeared flatter and smaller. The immune ring was considerably less dense. There was no anterior chamber reaction noted. Of concern, there was a small symblepharon noted at the lateral canthus, right eye. The cultures continued to show no growth of bacterial or fungal colonies and the polymerase chain reaction assay result was negative. The moxifloxacin and tobramycin/dexamethasone were reduced to 3 times a day, alternating right eye. He was scheduled for a 2-week follow-up visit.

The patient presented with mild complaints of itching but increased comfort overall in both eyes. He had reduced

the moxifloxacin and tobramycin/dexamethasone to twice a day, alternating every 6 hours. He restarted the tacrolimus 0.03% ointment around the eyelids in both eyes. He was using preservative-free artificial tears as needed in both eyes.

Biomicroscopy showed a closed corneal defect with a remnant infiltrate. The immune ring had dissipated. The bulbar conjunctiva had trace chemosis and injection. The overall appearance of the left eye was unchanged with persistent large palpebral papillae on the upper lids. There was minimal excoriation noted of the periocular skin. The intraocular pressure was 18 mm Hg in the right eye and 15 mm Hg in the left eye. There was no bacterial or fungal growth in the final culture assessment.

The moxifloxacin and tobramycin/dexamethasone were discontinued. The patient was placed on fluoromethalone 0.1% once a day for maintenance in the right eye for 2 weeks. The patient was instructed to use olopatadine 0.7% once a day in both eyes and artificial lubricants consistently. He was to continue to use the tacrolimus 0.03% ointment every other day on the periocular skin. He was scheduled for a 6-week follow-up examination.

The patient presented for the 6-week follow-up examination with minimal itching and irritation symptoms. He reported compliance with his medications and was using tacrolimus 0.03% ointment twice a day and olopatadine 0.7% once a day in both eyes. He uses cool compresses as needed and preservative-free artificial tears.

The examination showed uncorrected visual acuities of 20/25 in the right eye and 20/25 in the left eye. Slit lamp examination demonstrated lessening of the papillary response with minimal inferior corneal staining. The eyelid erosions had healed, and there was less edema and scaling. The intraocular pressure was 14 mm Hg in the right eye and 15 mm Hg in the left eye. There were no changes to the lens or posterior segment structures.

The patient was instructed to continue use of the tacrolimus 0.03% ointment once a day to eyelids and olopatadine 0.7% once a day, both eyes. Supportive treatment with lid hygiene, cool compresses, and artificial lubrication was emphasized. Compliance with the medication schedule was stressed. He was scheduled for a 6-month comprehensive visit.

DISCUSSION

Dupilumab is a fully human monoclonal immunoglobulin G antibody that blocks the shared interleukin 4 and interleukin 13 receptor, thus antagonizing the effects of these atopic mediators.[12] Specific to atopic dermatitis, interleukin 4 and interleukin 13 are involved in barrier function and the development of xerosis, pruritus, and lichenification.[1] In moderate to severe atopic dermatitis, systemic immunosuppression is necessary. Commonly, cyclosporine, steroids, and methotrexate are used to improve quality of life. Alternatively, biologics offer an advantage over these traditional therapies in atopic dermatitis through clearer skin, less pruritis, better sleep, and less side effects.[1] Dupilumab received US approval for the treatment of atopic dermatitis in 2017. It is also approved for moderate to severe asthma, prurigo nodularis, and its efficacy has been shown in chronic rhinosinusitis with nasal polyps and eosinophilic esophagitis.[13]

The most common dupilumab-associated ocular surface disease findings includes blepharitis and tarsal inflammation. About 25% of patients had limbal inflammation.[14] A review of the literature through June 2021 found the incidence of ocular surface disease associated with dupilumab varied from 8% to 26%.[3] These early studies did not evaluate for preexisting ocular surface disease prior to starting dupilumab.[3] A newer prospective study did evaluate for preexisting disease and found dupilumab-associated ocular surface disease developed in 28.9% of participants and was the most common adverse reaction associated with dupilumab in the treatment of atopic dermatitis.[14] Onset of dupilumab-associated ocular surface disease occurs at 2 to 16 weeks, plateaus at 20 to 24 weeks, and is rare after 44 weeks following the start of dupilumab.[12,15]

Although corneal ulcers are known to occur with atopic eye disease, there are limited reports on corneal ulceration believed related to dupilumab-associated ocular surface disease.[7-11] The cases associated with dupilumab vary in presentation and clinical signs. Two presented as bilateral peripheral ulcerative keratitis, two as paracentral defects that progressed to perforation, and another as a perilimbal infiltrate with corneal thinning. The pathogenesis has been speculated as either progressive atopic disease exacerbated by the dupilumab or an inflammatory reaction from resident flora enterotoxin.

None of the cases reported showed culture-positive infectious pathogens. Although this case presented similar to an infectious keratitis, the negative culture results and course with treatment does in part support a link to the use of dupilumab. Although the patient did not comply with the previous management, this patient also did not have the severe and rapid atopic keratoconjunctivitis changes, such as the increase in papillae, symblepharon, and the corneal ulceration, seen prior to beginning the dupilumab. This case is also consistent with the reported timelines of development of corneal ulceration that was reported to be between 2 and 12 weeks after beginning dupilumab. All cases, including this one, had between 1 and 2 dosages prior to onset of dupilumab-associated ocular surface disease.

Corneal ulceration is uncommon in atopic keratoconjunctivitis as well, with a retrospective study showing and incidence rate of 1.26%.[7] The vast majority were linked to infectious pathogens, including *Staphylococcus aureus* or *Streptococcus* species.[16-18] Atopic blepharitis has also been reported to be associated with increased risk of developing herpes simplex virus keratitis.[19]

Dupilumab-associated ocular surface disease is unique to atopic dermatitis for reasons unknown and not in the other Food and Drug Administration–approved uses. A review of multiple randomized clinical trials evaluating adverse side effects of dupilumab in the treatment of atopic conditions showed a higher incidence of conjunctivitis in atopic dermatitis compared with asthma and nasal polyposis groups.[12] A proposed hypothesis is the inhibition of interleukin 4 results in a shift from T-helper cell 2- to T-

helper cell 1–mediated inflammatory response, which exacerbates the chronic allergic T-helper cell 1 ocular inflammation associated with atopic dermatitis, as shown by the T-helper cell 1-associated elevated interferon-γ in tears.[15]

The pathogenesis of dupilumab-associated ocular surface disease is unknown but under investigation. Various hypotheses exist. Theories include a possible preexisting disorder, that is atopic keratoconjunctivitis, or a barrier dysfunction unique to atopic dermatitis and less common in other atopic diseases.[12] Studies support that dupilumab-associated ocular surface disease may be a result of a reduction in goblet cells and mucin production.[3] Interleukin 13 has been observed to increase goblet cell density and induce goblet cell differentiation, and its inhibition may cause goblet cell dysfunction and altered mucin production.[1] Consistent with this theory is the higher risk of conjunctivitis with other interleukin 13 monoclonal antibodies, tralokinumab and lebrikizumab, used in atopic dermatitis treatment.[1] Additionally, dupilumab-associated ocular surface disease was noted to improve when a Janus kinase inhibitor, ruxolitinib, was substituted for dupilumab.[14] In a recent study, dupilumab did not reduce the overall number of goblet cells in dupilumab-associated ocular surface disease, but it did reduce the secretion of mucin5AC. Mucin5AC is the main gel-forming glycoprotein produced by goblet cells.[14] This study also found lower median goblet cell numbers in both patients with more severe baseline atopic dermatitis and more severe dupilumab-associated ocular surface disease, suggesting low goblet cell density related to more severe ocular surface disease overall in atopic dermatitis.

The development of antidrug antibodies is another consideration based on research showing a higher incidence of ocular side effects that inversely correlates with lower serum levels of dupilumab and lower drug efficacy.[1] However, findings in the SOLO-CONTINUE study do not support antidrug antibodies as the cause of dupilumab-associated ocular surface disease.[20,21] The study also evaluated antidrug antibody levels across various treatment dosages and intervals. Results demonstrated an inverse correlation between treatment-emergent atopic dermatitis incidence and both dose and treatment interval with dupilumab, yet rate of conjunctivitis was low for all groups.[20]

Additional potential mechanisms suggest dupilumab-associated ocular surface disease pathophysiology is multifactorial. These include *Malassezia* colonization causing T-helper cell 17–driven dermatitis similar to seborrheic dermatitis, T-helper cell 1/T-helper cell 17 polarization, *Demodex* proliferation, and increased OX40 ligand activity.[15] Some suggest dupilumab-associated ocular surface disease results from exacerbation of underlying allergic disease. However, biopsies of dupilumab-associated ocular surface disease patients did not show histological features of allergy, suggesting dupilumab-associated ocular surface disease is a separate entity from atopic keratoconjunctivitis.[15]

Treatment of atopic keratoconjunctivitis includes artificial tears, cool compresses, and lid hygiene. Topical ophthalmic mast cell stabilizers and topical antihistamines provide relief for itch. Topical immunosuppression, and systemic for severe cases, is necessary to address the inflammation.

In early cases of dupilumab-associated ocular surface disease, clinicians often advocated discontinuation of dupilumab. Newer evidence indicates dupilumab-associated ocular surface disease resolves with continuation of dupilumab in 80% of cases.[12] Early treatment with anti-inflammatory medications minimizes the development of dupilumab-associated ocular surface disease. Tacrolimus ointment for external eyelids is frequently used, and a lower incidence of dupilumab-associated ocular surface disease is seen with use of anti-inflammatory treatment compared with nontreated or topical antihistamine use alone.[14] There are no standard guidelines for the management of dupilumab-associated ocular surface disease, but a proposed algorithm includes a baseline eye examination prior to initiation of dupilumab, patch testing, and regular surveillance.[15] However, cost-effectiveness and inconvenience of multiple visits may limit the practicality of this approach.

A different biologic, tralokinumab-ldrm (Adbry, LEO Phama, Inc) was approved in 2021 for the treatment of moderate to severe atopic dermatitis in pediatric patients aged 12 to 17 years. Like dupilumab, tralokinumab is associated with an increased occurrence of conjunctivitis. A study showed that the incidence was 7.5%, with most cases being mild or moderate. A majority of the cases resolved within the 16-week period of the trial. Increased risk of conjunctivitis occurred in patients who had more severe atopic dermatitis and an history of atopic keratoconjunctivitis.[22]

CONCLUSION

Mechanisms in which dupilumab causes or exacerbates ocular surface disease are yet to be determined. Corneal ulceration, whether infectious or immune related, is a rare but possible complication that may be associated with the use of dupilumab. To distinguish between atopic keratoconjunctivitis and dupilumab-associated ocular surface disease, baseline evaluation prior to initiation of dupilumab would be necessary. Most cases allow for continuation of dupilumab with topical treatment with anti-inflammatories, mast-cell stabilizers, and preservative-free artificial lubricants. Fortunately, most cases of dupilumab-associated ocular surface disease are mild, manageable, and temporary.

TAKE HOME POINTS

- Dupilumab increases the risk of ocular surface disease in patients with atopic dermatitis.
- Early recognition and treatment with topical corticosteroids or mast cell stabilizers is essential to decrease the development of long-term complications.
- Corneal ulceration is rare but must be distinguished between infectious vs inflammatory causes.

- It is critical to establish communication with dermatology to monitor for ocular signs while receiving therapy.

DISCLOSURES

None of the authors have a financial interest in the medications or products discussed in the manuscript.

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CLINICAL INSIGHTS IN EYECARE
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Haynes J, Steele R. Point-Counterpoint: To Treat or Not to Treat? Using Anti-Vascular Endothelial Growth Factor for Severe Nonproliferative Diabetic Retinopathy Without Macular Edema. *Clinical Insights in Eyecare*. 2024;2(2).

Point-Counterpoint

Point-Counterpoint: To Treat or Not to Treat? Using Anti-Vascular Endothelial Growth Factor for Severe Nonproliferative Diabetic Retinopathy Without Macular Edema

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Clinical Insights in Eyecare

Vol. 2, Issue 2, 2024

INTRODUCTION

Diabetes mellitus is a growing public health concern worldwide. It is estimated that 400 million people currently live with diabetes, which is projected to increase to almost 600 million by 2035.[1,2] Diabetic retinopathy (DR), a microvascular occlusive disease, is the leading cause of blindness among the working-age population.[2] Among diabetic individuals, the estimated prevalence of DR and proliferative DR (PDR) is 35.4% and 7.5%, respectively, with higher prevalence in type 1 diabetics.[1] Historically, intervention in DR was reserved for patients at high risk of vision loss, including patients with PDR with high-risk characteristics or patients with center-involving diabetic macular edema (CI-DME). Patients with nonproliferative disease without macular edema have historically been managed with close observation, lifestyle modifications, and strict control of blood glucose levels and systemic vascular disease. Recent investigations into early intervention with anti- vascular endothelial growth factor (VEGF) in patients with severe nonproliferative DR (NPDR) without macular edema have raised the question of whether early intervention may be warranted to prevent long-term progression of disease and potentially reduce the risk of vision-threatening complications.[3,4] No identifiable health information was included in this case report.

CASE INFORMATION

CASE HISTORY

- White male, age 47 years
- Referred for diabetic eye examination by a fellow optometrist
- No significant complaints aside from decreased near vision corrected with reading glasses
- Type 2 diabetes for 10 years, with most recent A1C of 9.7% 2 months prior. Does not check blood sugar at home. Managed with weekly Trulicity injections.
- Additional history of hypertension and hyperlipidemia

Other pertinent examination findings

- Distance visual acuity 20/20 right eye, left eye
- Normal anterior segment evaluation with no neovascularization of the iris of each eye
- Presence of significant retinal hemorrhaging in all 4 quadrants of each eye. Presence of intraretinal microvascular abnormalities along the superior temporal arcade of the left eye (Figure 1).
- Absence of CI-DME on optical coherence tomography (Figure 2).

DIAGNOSIS

- Severe NPDR without macular edema in each eye

POINT: TREATMENT OF SEVERE NPDR WITH ANTI-VEGF

By Jessica Haynes, OD, FAAO

A patient such as this must be educated about the importance of maintaining good blood sugar control, as well as managing concomitant vascular disease, including hypertension and hyperlipidemia. Education is required to understand that although the patient is currently asymptomatic and has good visual acuity, significant damage has already occurred to the retinal vasculature, and the patient is at risk for vision loss due to complications such as macular edema and development of PDR. Although a patient with severe NPDR without macular edema could be monitored closely at 3 to 4 month intervals without intervention, in a highly motivated and educated patient, initiation of anti-VEGF injections has been shown to reduce their level of DR and decrease the occurrence of sight-threatening complications, including CI-DME.[3,4]

The PANORMA study, a 100-week randomized clinical trial, compared the outcomes of moderately severe to severe NPDR without macular edema treated with intravitreal aflibercept vs sham injections.[3] A total of 402 individuals were randomly assigned into 3 cohorts. A total of 135 eyes received intravitreal aflibercept 2 mg every 16 weeks after 3 loading monthly injections and one 8-week interval. A total of 134 eyes received intravitreal aflibercept 2 mg every 8 weeks after 5 loading monthly injections followed by as needed (PRN) treatment between year 1 and 2 based on DR severity score (DRSS). A total of 133 eyes received sham injections, receiving treatment only if sight-threatening complications arose.

The major outcome measures included a 2-step improvement in DRSS, occurrence of vision-threatening complica-

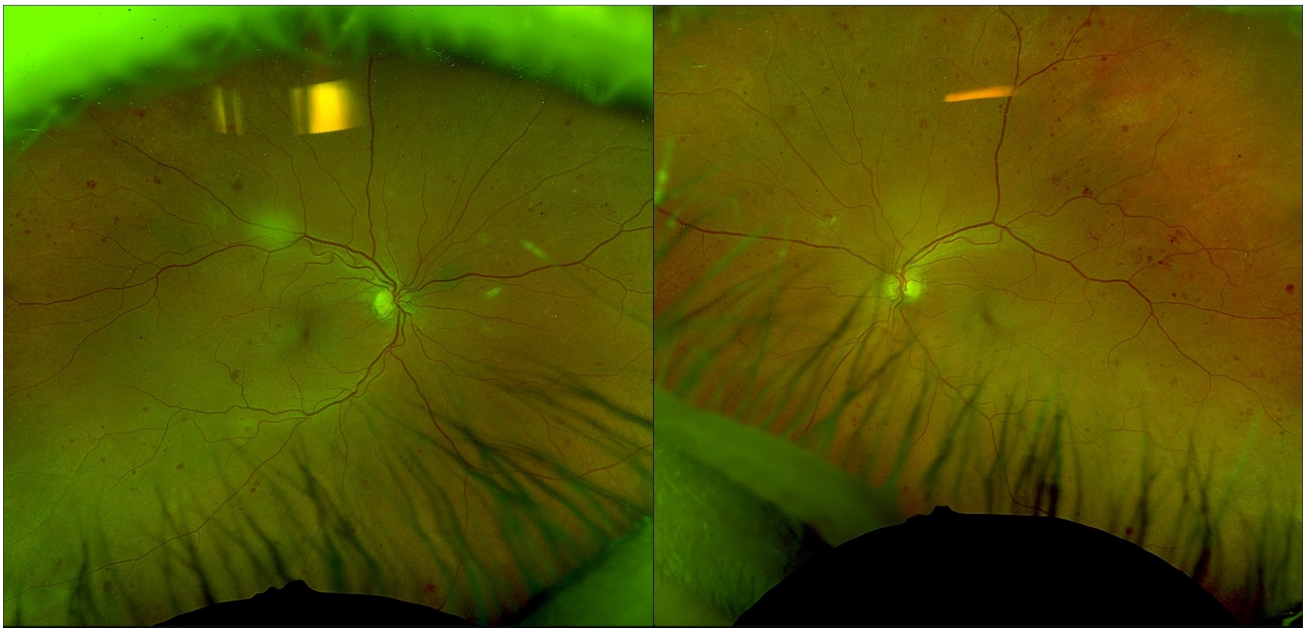

Figure 1. Significant retinal hemorrhages in all 4 quadrants of each eye with intraretinal microvascular abnormalities along the superior temporal vascular arcade in the left eye constitutes a diagnosis of severe nonproliferative diabetic retinopathy in each eye.

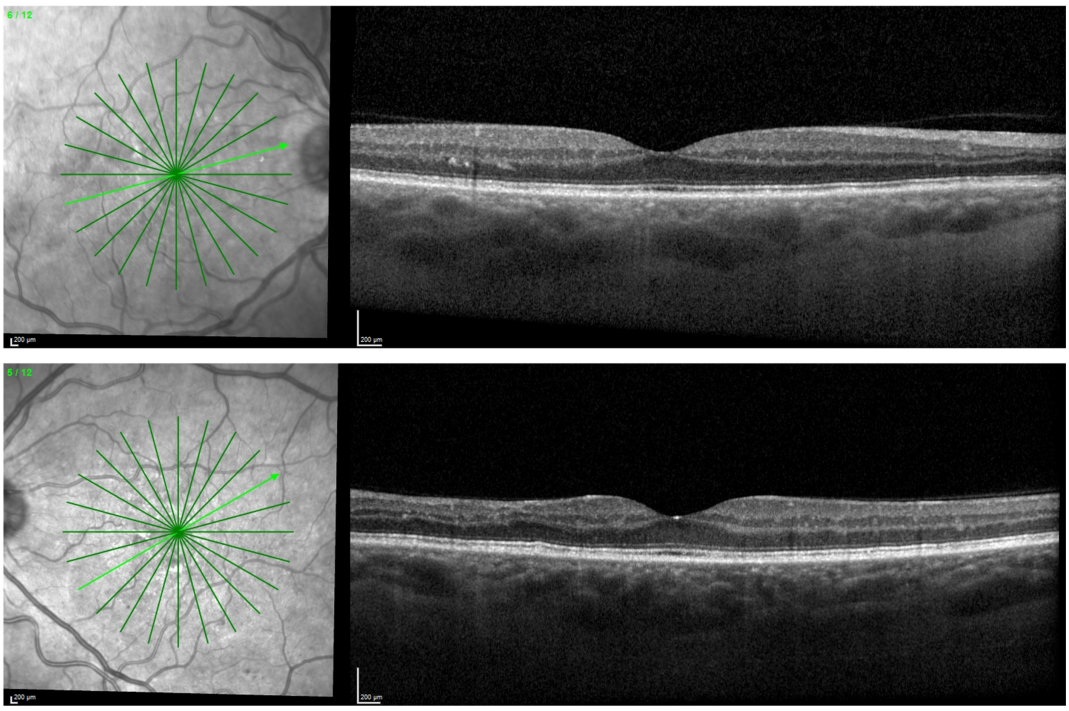

Figure 2. Optical coherence tomography of the macula confirms absence of macular edema in each eye.

tions (including complications of PDR and iris neovascularization), and occurrence of CI-DME. After 100 weeks, the authors concluded that receiving intravitreal aflibercept 2mg significantly improved DRSS. At 100 weeks, 62.2% of patients treated every 16 weeks had a 2-step reduction in their DRSS, as did 50% in the every-8-weeks/PRN group. This was compared with only 12.8% of patients receiving sham.

In addition, treatment with aflibercept significantly reduced vision-threatening complications and the development of CI-DME compared with those receiving sham injections. At 100 weeks, 50.4% of eyes in the sham group developed vision-threatening complications and/or CI-DME vs only 16.3% in the every-16-weeks treatment group and 18.7% in the every-8-weeks/PRN treatment group.

With these striking results, a patient such as the one above can be educated that by receiving intravitreal injec-

tions every 16 weeks (about every 4 months following a loading dose), we have a 60% chance to significantly reduce his or her level of DR, and we can take the chance of developing sight-threatening complications from 50% down to only about 16%. It is important to note that compliance with treatment is extremely important and that although risk of sight-threatening complications is much lessened, it is not totally eliminated. Thus, there is still importance of close follow-up and adjustment of treatment if needed.

COUNTERPOINT: MONITOR WITHOUT TREATMENT

By Rachel Steele, OD

Although this patient remains a good candidate for treatment with anti-VEGF per the outcomes of the PANORAMA trial, controversy exists over whether earlier initiation of anti-VEGF truly translates into long-term improvement in visual outcomes. The main outcome of 2-step reduction in DRSS in the PANORAMA trial has been criticized as improving a clinical picture but not ultimate visual outcomes. In addition, requirement for long-term compliance, greater treatment burden, risk of side effects from injections, and loss of benefit with discontinuation of treatment are all downsides for use of anti-VEGF in those with severe NPDR.

In post hoc analyses of PANORAMA, of the eyes that developed vision-threatening complications, a greater percentage of eyes randomized to the control group went on to lose 5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters compared with those randomized to aflibercept; however, the authors noted that discontinuation of aflibercept injections or less frequent injections "may lead to PDR-related complications,"[3] and suggested that regular treatment intervals were necessary to maintain DRSS improvement and decrease the risk of vision-threatening complications. Ultimately, there was no significant difference in visual acuity between eyes that were treated with aflibercept vs sham injections after 2 years. However, this requires careful monitoring and initiation of treatment should sight-threatening complications arise.

The Diabetic Retinopathy Clinical Research Network similarly evaluated treatment of moderate to severe NPDR without CI-DME in Protocol W.[4] Eyes were randomized to receive either aflibercept 2 mg or sham injections at 1, 2, and 4 months and then every 4 weeks for 2 years. Of 399 participants, 200 eyes were randomized to receive aflibercept 2 mg and 199 eyes received sham injections. The study's main outcome measures were development of either PDR or CI-DME. Results of the study showed that eyes randomized to aflibercept 2 mg had a significantly lower probability of developing PDR or CI-DME at 2 years. Additionally, a greater percentage of eyes receiving aflibercept 2 mg had a 2-step improvement in DRSS compared with the sham group. However, similar to PANORMA, the study concluded that regular treatment with aflibercept 2 mg did not "confer visual acuity benefit compared with observation with aflibercept 2mg initiated only after development of PDR or CI-DME."[4] The authors remarked that careful observation with treatment after development of vision-threatening complications may be sufficient to either recover vision loss or prevent vision loss.

More recently, data from the 4-year extension of Protocol W became available.[5] After 4 years, the likelihood of developing PDR in the aflibercept 2 mg group was 27.9% vs 49% in the sham group. The probability of developing CI-DME was 11.3% in the aflibercept group vs 19.1% in the sham group. Similar to the 2-year Protocol W and PANORAMA studies, there was a greater improvement in DRSS in the aflibercept 2 mg group. But still, there was no significant difference in visual acuity outcomes between the 2 groups at 4 years. The authors concluded that based on the evidence gained from the study, there was no evidence to suggest that early treatment intervention in nonproliferative retinopathy without macular edema conferred any visual benefit out to 4 years when compared with close observation and treatment when vision-threatening complications arose. Although early treatment did reduce the risk of development of PDR and CI-DME, it did not eliminate the likelihood of progression.[5]

Although early intravitreal anti-VEGF was shown to decrease the risk of future vision-threatening complications, treatment needs to be maintained at regular intervals to remain beneficial, which may add to the overall treatment burden for patients. Although both PANORAMA and Protocol W demonstrated that early anti-VEGF improves DRSS, there is debate over whether improvement in DRSS truly represents improvement in overall disease.[3,5-7] Recent studies by Couturier et al and Bonnin et al demonstrated that intravitreal anti-VEGF, though stabilizing the permeability of retinal microvasculature, does not result in reperfusion of ischemic capillary beds. DR lesions such as microaneurysms or intraretinal hemorrhages, though a sign of ongoing microvascular disease, do not present the greatest risk for progression to PDR. Ischemia and capillary nonperfusion drive progression to proliferative disease. Despite improvements in DRSS, which accounts for the number of DR lesions, these patients are still at risk of proliferative disease because areas of nonperfusion remain despite treatment.

Because of the long-term results of Protocol W, a patient such as this can be educated that although earlier intervention is an option, there is ultimately no evidence of altered long-term visual outcomes. Although treatment can be deferred for this patient at the time being, success still critically hinges on close observation and prompt initiation of treatment should sight-threatening complications arise. This must be heavily emphasized to the patient alongside the importance of improved blood sugar control and control of concomitant vascular disease.

SHOULD LASER BE CONSIDERED FOR SEVERE NPDR?

Pan-retinal photocoagulation (PRP) is regarded as the standard of care for individuals with PDR.[8] PRP is thought to control retinal or anterior segment neovascularization by destroying metabolically active retinal tissue, which de-

creases the overall oxygen demand from the tissue by reducing proangiogenic factors.[8,9] PRP has long been reserved for patients with proliferative disease to reduce the long-term risk of vision loss from complications of proliferative disease rather than improve vision.

The Diabetic Retinopathy Study (DRS) and ETDRS investigated the use of PRP in nonproliferative retinopathy. In the DRS, patients had one eye receive PRP and one eye as control. At 2 years, the overall risk of severe vision loss was 3.2% in the control eyes vs 2.8% in the eyes with PRP.[9] Although they found that a greater portion of the eyes without PRP went on to develop proliferative disease within the year, they did not recommend PRP for all patients with NPDR. Because of the risk of severe vision loss being low between the treated and untreated severe NPDR groups, and because of the side effects of PRP treatment such as loss of peripheral vision, the investigators recommended reserving PRP for eyes with PDR with high-risk characteristics.

In the ETDRS, patients with severe NPDR had one eye receive PRP and the other eye defer PRP. The eyes with deferred PRP had significantly higher rates of conversion to PDR at 1, 3, and 5 years; however, at 5 years, the comparison of severe vision loss between the early and deferred PRP groups was 2.6% and 3.7%, respectively.[10] Although the risk of severe vision loss was similar between the groups, the ETDRS group did suggest that prophylactic PRP could be considered in select individuals with severe NPDR.

PRP leads to destruction of retinal tissue that can translate into loss of peripheral vision and reduction in night vision. Even in PDR, the use of heavy PRP has lessened significantly because of the ability to supplement with anti-VEGF. Although the utilization of PRP in those with severe NPDR is significantly less than in those with PDR, some physicians may still use the tactic in select patient populations with severe NPDR, such as those who cannot maintain compliance with follow-up or those who have had poor outcomes from PDR in the fellow eye or found it difficult to control PDR in the fellow eye.

With our current patient, PPR was not recommended by either provider.

CONCLUSIONS

Translating the results of these trials to everyday practice presents significant challenges for the practitioner, given that many patients do not understand the significant risk of future worsening in their vision or the necessity of frequent careful observation. In every treatment decision, there must be an individualized discussion with the patient about the risk presented by their disease and the potential risks and benefits conferred by any treatment intervention. Although PANORAMA and Protocol W demonstrated that early treatment with anti-VEGF reduced the rates of disease progression, they did not demonstrate that there was any visual benefit conferred by early treatment, at least up to 4 years.

Considerations for treatment initiation with anti-VEGF in those with severe NPDR without macular edema include patient preferences, blood sugar control, systemic comorbidities, ability to comply with treatment, ability to comply with follow-ups, financial obligations, and side effects of treatment. Although earlier treatment initiation is an option, given the lack of long-term improvement in visual acuity outcomes, practitioners may also continue managing these patients with frequent careful observation.

DISCLOSURES

Dr Haynes is a paid speaker for Heidelberg Engineering and Zeiss. She is a consultant for Regeneron. Dr Steele has no financial disclosures.

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CLINICAL INSIGHTS IN EYECARE
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THE DOUBLE LAYER SIGN IS HIGHLY PREDICTIVE OF PROGRESSION TO EXUDATION IN AGE-RELATED MACULAR DEGENERATION

Csincsik L, Muldrew KA, Bettiol A, et al. The Double Layer Sign Is Highly Predictive of Progression to Exudation in Age-Related Macular Degeneration. Ophthalmol Retina. 2024;8(3):234-245. doi:10.1016/j.oret.2023.10.006Csincsik L, Muldrew KA, Bettiol A, et al. *Ophthalmology Retina*. Published online October 13, 2023. doi:10.1016/j.oret.2023.10.006

QUESTION

Is the presence of a double-layer sign and a shallow irregular retinal pigment epithelium elevation able to predict progression to exudative macular neovascularization in the unaffected fellow eyes of patients with age-related macular degeneration recently diagnosed with unilateral exudative macular neovascularization?

BACKGROUND/SUMMARY OF FINDINGS

Exudative macular degeneration is a sight-threatening condition that can remain undetected on its first occurrence unilaterally, and even when the patient is aware of their first eye having exudation, they may be unaware of changes that arise in the fellow eye. As early treatment is critical toward preserving macular structural integrity and central vision, identifying eyes at risk of progressing to exudative disease becomes an even more critical first step in the treatment and preservation process. Spectral domain optical coherence tomography and optical coherence tomography angiography are powerful tools that can be used to capture macular tissues affected by age-related macular degeneration. However, optical coherence tomography angiography is neither as universally available in routine clinical practice nor as well understood as traditional spectral domain optical coherence tomography. Therefore, the ability to detect features/biomarkers consistent with exudative disease, as well as features that may predict the development of exudative macular degeneration, that can be specifically captured on conventional optical coherence tomography would be beneficial.

Recent spectral domain optical coherence tomography studies have detected dormant layers of blood vessels between the retinal pigment epithelium and its basement membrane, vessels that show no overt signs of exudation. Even more clearly delineated through the use of optical coherence tomography angiography and labeled as nonexudative macular neovascularization, these vessel layers are associated with a low-lying elevation of the retinal pigment epithelium on optical coherence tomography B scan analysis. Initially this low-lying elevation of the retinal pigment epithelium was known as the double-layer sign and defined by the presence of a highly reflective inner layer consisting of the retinal pigment epithelium and coupled with an additional highly reflective outer layer composed by Bruch's membrane. The initial double-layer sign characteristics were refined to include length and height dimensions (≥1000 μm in length and <100 μm in height) and ultimately became known as the shallow irregular retinal pigment epithelium elevation sign.

In this retrospective reanalysis of 3 years of follow-up spectral domain optical coherence tomography scan data from the Early Detection of Neovascular AMD study, the values of irregular elevations, double-layer sign, and shallow irregular retinal pigment epithelium elevation signs in predicting progression to exudative macular neovascularization were respectively assessed.

The authors found that when study eyes were grouped by the presence of irregular elevations, double-layer sign, or shallow irregular retinal pigment epithelium elevation, all three features/biomarkers increased the risk of progression to exudative macular neovascularization, with the highest rate of progression (41% of patients progressing to exudative macular neovascularization over 3 years) and four times greater hazard of exudative macular neovascularization in patients with the double-layer sign. Interestingly, fulfilling the more specific optical coherence tomography moniker of shallow irregular retinal pigment epithelium elevation did not increase the predictive value for progression to exudative macular neovascularization. The authors concluded pragmatically that the dimensions of the double-layer sign are less important than its presence alone and that patients with these irregular elevations should be surveilled more closely with spectral domain optical coherence tomography and with optical coherence tomography angiography if available.

CLINICAL VALUE/IMPLICATIONS

The evolution of optical coherence tomography in characterizing diseases of the eye has led to an increasingly complicated nomenclature that is constantly evolving and often difficult to keep abreast of in clinical practice. This study supports that it is likely more critical to be able to recognize the presence of and even qualitative aspects of various optical coherence tomography biomarkers, rather than obsess over achieving certain quantitative dimensions in order to

use these biomarkers prognostically. The double-layer sign is an important biomarker that we all should be aware of when managing our patients with age-related macular degeneration.

PROGNOSTICATION IN STARGARDT DISEASE USING FUNDUS AUTOFLUORESCENCE: IMPROVING PATIENT CARE

Daich Varela M, Laich Y, Hashem SA, Mahroo OA, Webster AR, Michaelides M. Prognostication in Stargardt Disease Using Fundus Autofluorescence: Improving Patient Care. Ophthalmology. 2023;130(11):1182-1190. doi:10.1016/j.ophtha.2023.06.010

QUESTION

Can fundus autofluorescence provide a useful surrogate to conventional electrodiagnostic testing for classifying Stargardt disease?

BACKGROUND/SUMMARY OF FINDINGS

Stargardt disease is a common genetic retinal dystrophy. Prognosis of the condition is highly variable depending on the phenotype and is tied relatively tightly to classification with electroretinography. The mildest stage—group ERG1—shows severe abnormality of macular function and normal full-field peripheral function. Group ERG2 demonstrates severe macular dysfunction with additional generalized cone dysfunction. Group ERG3 demonstrates the same findings as group ERG2 with the addition of generalized rod dysfunction. Within this classification system, group ERG1 has a relatively good prognosis, ERG2 has a variable prognosis, and ERG3 has a poor prognosis. Furthermore, these groups are generally stable over time. Although electroretinography correlates well with prognosis, it is not widely available, is dependent on patient and center reliability, and is somewhat invasive. This review looks at whether fundus autofluorescence would be a reliable surrogate for ERG in the management of disease in patients with Stargardt disease.

This single-center retrospective review looked at 234 patients who had been monitored for Stargardt disease, had been classified with electrodiagnostic, and who also had ultra-widefield fundus autofluorescence performed to assess for agreement between fundus autofluorescence and electroretinography staging. The patients were categorized into groups based on fundus autofluorescence characteristics. Fundus autofluorescence 1 showed only central hypo autofluorescence, fundus autofluorescence 2 showed central hypo autofluorescence and a heterogeneous background, and fundus autofluorescence 3 was defined as having multiple areas of hypo autofluorescence within the posterior pole as well as a heterogeneous background. The review found that, in general, fundus autofluorescence staging corresponded with electrodiagnostic staging, with fundus autofluorescence matching electrodiagnostic staging 73% of the time. The 27% where fundus autofluorescence and electrodiagnostics disagreed was evenly split between fundus autofluorescence overestimating 13% of patients' disease stages compared with electrodiagnostics and underestimating 14%. The greatest variability between fundus autofluorescence and electrodiagnostics was in very young patients (10 years old or younger). Subgroup analysis comparing ultra-widefield fundus autofluorescence with 30° and 55° fundus autofluorescence showed 97% and 98% agreement.

CLINICAL VALUE/IMPLICATIONS

This review shows reasonable agreement between an objective, noninvasive, widely available technology—fundus autofluorescence—and the subjective, less available technology with greater potential for intertest variability—electrodiagnostics—in assessment and prognosis of patients with Stargardt disease. As such, fundus autofluorescence appears to be a useful surrogate for most patients with the disease. When managing children with Stargardt disease, electrodiagnostics may provide a superior level of confidence in prognosis.

EVALUATION OF THE CONSISTENCY OF GLAUCOMATOUS VISUAL FIELD DEFECTS USING A CLUSTERED SITA-FASTER PROTOCOL

Tan JCK, Phu J, Go D, et al. Evaluation of the Consistency of Glaucomatous Visual Field Defects Using a Clustered SITA-Faster Protocol. Ophthalmology. 2023;130(11):1138-1148. doi:10.1016/j.ophtha.2023.06.018

QUESTION

Can frontloading SITA-faster visual fields provide repeatable data that can be used to evaluate the consistency of pattern deviation defects in glaucoma?

BACKGROUND/SUMMARY OF FINDINGS

Although functional testing is an incredibly important aspect of glaucoma diagnosis and management, it exhibits a substantial amount of variability and requires a great deal of testing to minimize that variability in order to provide information sufficient to confidently determine whether glaucoma is or is not progressing. This requirement for a large amount of data results in a burden to both the patient and the perimetrist alike and contributes to a lack of real-world data acquisition when compared with published guidelines on the optimal number and frequency of visual fields necessary to make sound management decisions. The addition of the SITA-faster algorithm has greatly reduced the time required to acquire visual field data, and the authors of this paper recently determined that SITA-faster could be successfully clustered in the same visit, and that this clustering was acceptable to both patients taking and technicians administering the SFRs.

Using a prospective, cross-sectional study design, the authors acquired two SITA-faster tests on the same visit on

patients with suspected or confirmed glaucoma having undergone Sita-standard testing on a previous visit. Global sensitivity, reliability indices, and pointwise deviation map probability scores from the pattern deviation grid were compared across the three visual fields to evaluate the consistency of detecting the visual field defects. The authors found no significant difference in global sensitivity across the three fields or in the rate of obtaining at least one reliable test among the three. Notably, the frontloaded SITA-faster tests confirmed existing Sita-standard pointwise deviation defects in 62% of cases and reversed Sita-standard defects in 8.2%. Importantly, a new defect of at least three contiguous points was detected in 20.1% of eyes with the frontloading of SITA-faster tests.

The authors concluded that frontloading SITA-faster tests can provide repeatable data that can be used to determine the consistency of pattern deviation visual field defects, without being compromised by testing fatigue, and performing at a level equivalent to a single SITA-standard test. They mentioned that this might provide a new strategy by which an appropriate level of visual fields can be acquired while reducing the traditional burden involved in meeting established guidelines.

CLINICAL VALUE/IMPLICATIONS

Practice guidelines in glaucoma show that there is a consistently insufficient number of visual fields performed in order to determine whether progression of the disease has occurred. This lack of testing can result in a delayed ability to detect change and the rate of that change, leading to worse outcomes in faster progressors. The clustering of visual fields provide a potential new approach to help overcome this issue and, in this study, has been shown to be effective in a real-world glaucoma practice. These results could spark additional conversation about how functional testing can be optimized in our practices to best serve the needs of our patients with glaucoma.

MAINTENANCE OF VISION NEEDED TO DRIVE AFTER INTRAVITREAL ANTI-VEGF THERAPY IN PATIENTS WITH NEOVASCULAR AMD AND DIABETIC MACULAR EDEMA

Emami-Naeini P, Garmo V, Boucher N, Fernando R, Menezes A. Maintenance of Vision Needed to Drive after Intravitreal Anti-VEGF Therapy in Patients with Neovascular Age-related Macular Degeneration and Diabetic Macular Edema. Ophthalmol Retina. Published online October 20, 2023. doi:10.1016/j.oret.2023.10.010

QUESTION

What is the association between intravitreal anti–vascular endothelial growth factor injections and visual acuity/driving in patients with neovascular age-related macular degeneration or diabetic macular edema?

BACKGROUND/SUMMARY OF FINDINGS

Neovascular age-related macular degeneration and diabetic macular edema are both common causes of central vision loss, which can negatively impact patients' ability to drive, subsequently affecting their independence and quality of life. Driving cessation specifically has been associated with decreased mobility and out-of-home activities, depression, greater risk of entry into a long-term care facility, and increased risk of mortality. Although the addition of anti–vascular endothelial growth factor agents has substantially improved both anatomical and visual outcomes, the burden of treatment is high.

This was a retrospective, observational, real-world cohort study of visual acuity and driving vision maintenance over time in patients with neovascular age-related macular degeneration and diabetic macular edema having received anti–vascular endothelial growth factor therapy using data collected from the Vestrum Health database between January 1, 2014, and June 30, 2019. The Vestrum database consists of electronic health record data obtained from more than 360 US retinal specialists.

Outcome measures were mean change in visual acuity over time and by baseline visual acuity, driving vision maintenance over time and stratified by injection frequency and baseline factors predictive of driving vision maintenance.

In the initial year of treatment, patients with neovascular age-related macular degeneration and diabetic macular edema gained, on average, 8.5 and 9.5 ETDRS letters, respectively. Between years 1 and 4, patients with neovascular age-related macular degeneration and diabetic macular edema lost 6.6 and 2.7 ETDRS letters, respectively. The probability of maintaining driving vision over 4 years was 56% in patients with neovascular age-related macular degeneration and 72% in those with diabetic macular edema. There was a dose-related response, and in patients receiving 1-5, 6-7 and ⩾8 anti–vascular endothelial growth factor injections in year 1, the corresponding probabilities of maintaining driving were 50%, 56%, and 65% in patients with neovascular age-related macular degeneration and 63%, 72%, and 77% in patients with diabetic macular edema. Baseline factors associated with driving loss included older age, worse index visual acuity, geographic atrophy, and worsening baseline diabetic retinopathy.

CLINICAL VALUE/IMPLICATIONS

This study supports early and frequent intervention with anti–vascular endothelial growth factor injections in patients with neovascular age-related macular degeneration and diabetic macular edema. These results provide us with important real-world data that can be used to inform our conversations with patients who have concerns of losing their ability to drive and, subsequently, their independence. Advising them to commit to the recommended course of injections, especially early in the course of treatment, can help empower them to reduce their risk of vision loss.

PLACEBO EFFECT AND ITS DETERMINANTS IN OCULAR HYPOTENSIVE THERAPY. META ANALYSIS AND MULTIPLE META-REGRESSION ANALYSIS

Choe S, Kim YK, Chung W, et al. Placebo Effect and Its Determinants in Ocular Hypotensive Therapy: Meta-analysis and Multiple Meta-regression Analysis. Ophthalmology. 2023;130(11):1149-1161. doi:10.1016/j.ophtha.2023.06.012

QUESTION

Is intraocular pressure influenced by the placebo effect?

BACKGROUND/SUMMARY OF FINDINGS

The placebo effect has been identified in many surprising physiologic processes that go beyond subjective patient experiences. This large meta-analysis looks at 40 randomized clinical trials on ocular hypotensive treatments and their respective control groups to assess whether the placebo effect may exert an influence on intraocular pressure. Broadly, this review assessed the difference in intraocular pressure between placebo groups (those applying a non-treatment eye drop: n = 2055 eyes) and untreated eyes (n = 1184 eyes). The pretreatment intraocular pressure was compared with posttreatment intraocular pressure among the study group (those receiving true therapy) and control groups (comparing placebo treatments with nontreated control patients)

CLINICAL VALUE/IMPLICATIONS

Interestingly, a relatively robust placebo effect did materialize. Placebo treatment control individuals had, on average, 2.27 mm Hg lower intraocular pressure compared with untreated control individuals. Just as interesting, the degree of placebo effect seemed to be relative to the degree of intraocular pressure reduction in the actual treatment group. Placebo-treated patients achieved 0.45 mm Hg intraocular pressure reduction for every 1 mm Hg intraocular pressure reduction achieved by the actual treatment group. Finally, substudy analysis showed the magnitude of the placebo effect was related to the sample size assessed. Although interesting, results of this study are probably most appropriately confined to academic interpretation of efficacy studies on glaucoma treatments.