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Reversible bilateral central scotoma under scotopic conditions associated with oral semaglutide

Peter Bracha [a,*], William Johnson [a], Sabrina Chu [b], James Davison [a]

[a] Wolfe Eye Clinic, 6200 Westown Parkway, West Des Moines, Iowa, USA
[b] Des Moines University College of Osteopathic Medicine, 3200 Grand Ave, Des Moines, IA, USA

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ABSTRACT

Introduction: Semaglutide is a glucagon-like peptide-1 receptor agonist that treats type 2 diabetes mellitus and can be used as an adjunct for weight loss when combined with exercise and diet. Here we report a case of a bilateral, incongruent central visual scotoma under scotopic conditions in a board-certified ophthalmologist associated with semaglutide use that resolved quickly following medication discontinuation.

Case report: A 72-year-old male ophthalmologist (JAD) started 3.0 mg daily oral semaglutide (Rybelsus) to help with weight loss and seventeen days after treatment initiation developed a small, round central scotoma in his right eye that enlarged over several days. After two days a similar but smaller scotoma developed in his left eye. These symptoms were present only under scotopic conditions and were not visible in daylight or artificially lit conditions. When symptoms developed in the left eye, the medication was discontinued, and all symptoms completely resolved two days later. A subsequent clinical evaluation revealed no abnormalities on macular optical coherence tomography, fundus photography, fundus autofluorescence or Humphrey visual field.

Conclusions: This case of a bilateral central scotoma under scotopic conditions that resolved after medication discontinuation expands the knowledge of potential side effects from this increasingly popular diabetic and weight loss medication.

1. Introduction

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP1-RA) that treats type 2 diabetes mellitus and can also be used as an adjunct for weight loss when combined with exercise and diet.[1,2] It works by increasing insulin release and sensitivity, and is available in oral daily and weekly injection formulations. The use of semaglutide has increased in recent years, both due to its efficacy and popularity on social media.[3]

One ophthalmic side effect of semaglutide and similar GLP1-RAs is a paradoxical increase in diabetic retinopathy, possibly due to rapid blood sugar reduction.[4,5] Other reports of macular complications and blurred vision have been reported in federal reporting systems, which have various limitations.[6,7] Here we report a case of a central, bilateral visual scotoma under scotopic conditions in a board certified ophthalmologist (JAD), that resolved quickly following medication discontinuation. To our knowledge no prior similar case has been reported.

2. Case report

A 72-year-old board-certified male ophthalmologist (JAD) with a past medical history of atrial fibrillation and with an ocular history of cataract surgery with intraocular lens implantation (Alcon, +20.0D CNA0T0) in the right eye 18 months earlier for a standard nuclear sclerotic cataract, and a mild, not-visually-significant nuclear cataract on the left, started taking oral semaglutide to help with weight loss. Seventeen days after starting 3.0 mg oral semaglutide (Rybelsus) daily, the typical starting dose, he observed a small, round central scotoma in his right eye (Fig. 1). It appeared to enlarge over three evenings of observation, ultimately turning into an irregular square shape (Fig. 2). The scotoma was estimated to measure approximately 18° based on its 2-foot obscuration of the central portion of a 4-foot diameter ceiling fan from a distance of approximately 6 feet. After three days a similar but smaller scotoma was detected in his left eye.

These symptoms were observed only under scotopic conditions in a bedroom which had several windows, no curtains and lit dimly by moonlight. These symptoms were observed upon retiring to the

* Corresponding author. 6200 Westown Parkway, West Des Moines, IA, USA.
E-mail address: peterbracha@yahoo.com (P. Bracha).

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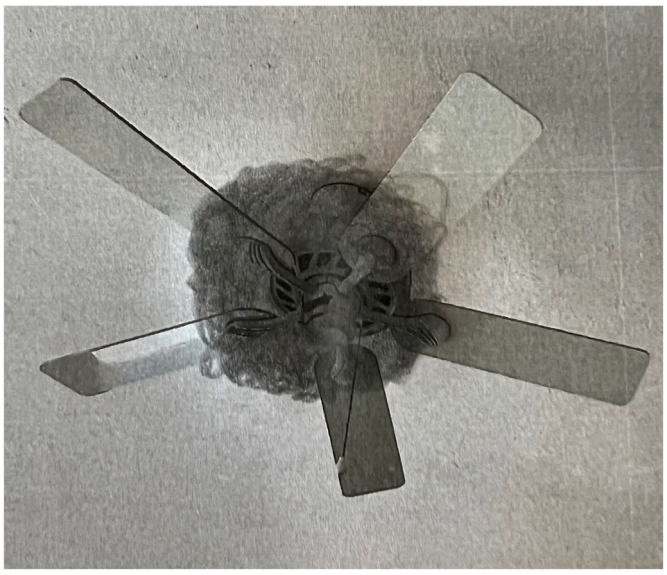

Fig. 1. Patient drawing of a right eye, dim scotoma under scotopic condition covering the central portion of a ceiling fan.

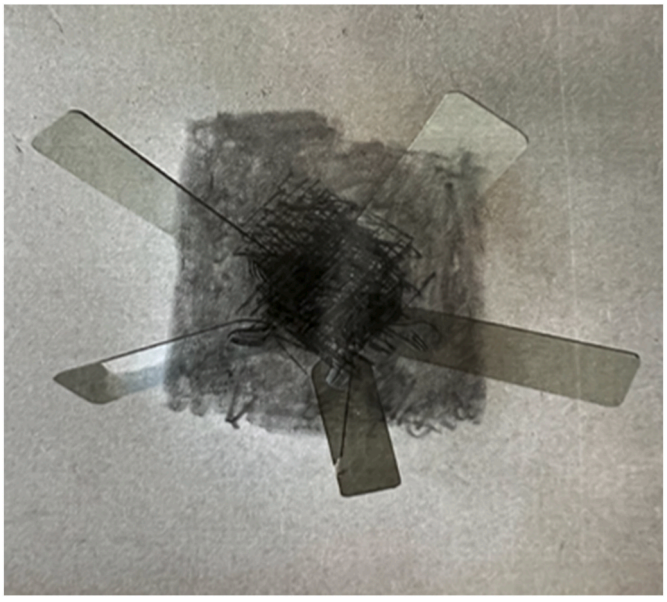

Fig. 2. The right eye scotoma grew in size over several evenings and became an irregular square-shape while the relative dimness of the scotoma remained unchanged.

bedroom, persisted throughout the night, were also present in a dimly lit hallway, and disappeared upon turning on a lamp and with the emergence of daylight the next morning. When closing his eyes, a bright white afterimage of the dark scotoma faded over 5 seconds, consistent with a physiologic afterimage.[8] When entering a partially lit bathroom, the scotoma took on a dark brown appearance for a fraction of a second and then disappeared.

A smaller and more subtle scotoma was observed in his left eye three evenings after the right had started. That next morning, a possible association with semaglutide was suspected and the medication was discontinued. The symptoms gradually diminished over the next two evenings and were gone thereafter. No similar episode had previously or subsequently occurred. The timing of symptoms is summarized in Table 1.

Other than minimal knee pain from a fall a week before, no changes to his health had preceded his visual symptoms. He denied any associated neurologic, autoimmune, psychiatric or other systemic changes. His medications included oral semaglutide 3 mg daily from April 5th, 2023 to April 25th, 2023, propranolol 20 mg twice a day, aspirin 81 mg daily, naproxen 220 mg and ibuprofen 400 mg as needed for knee pain. The patient returned from vacation in Florida to the Midwest, upon which a formal ophthalmic evaluation was performed two days after his symptoms had resolved. His uncorrected distance visual acuity measured 20/20 right eye (OD) and 20/25 left eye (OS). The anterior segment exam was benign including a well-centered intraocular lens and clear posterior capsule OD and a mild nuclear sclerotic cataract OS. Fundus examination demonstrated normal appearing optic nerves, scattered small drusen in each macula and vitreous opacities from a posterior vitreous detachment OS (Fig. 3). Humphrey visual field testing, 10-2, revealed a reliable test without evidence of visual field loss (Fig. 4). Macular optical coherence tomography identified subretinal drusenoid deposits with a poorly defined interdigitation zone (IZ) in the fovea but preserved IZ elsewhere in the macula (Fig. 5), similar in appearance to scans years before and prior to any symptoms. Retinal nerve fiber layer OCTs were normal.

Table 1
Timeline of events following administration of oral 3 mg Semaglutide.

Date	Event
Day 0	Started 3.0 mg semaglutide in the morning
Day 16	First noticed right eye round, central scotoma
Day 17	Noticed enlarging square scotoma including and just below fixation
Day 19	Noticed a minimal, small and round scotoma in the left eye
Day 20	Discontinued semaglutide with 10 doses remaining (20 days total)
Day 21	Rounds scotomas persist both eyes
Day 22	Noticed an enlarged scotoma right eye covering a door panel
Day 23	Residual scotomas remain
Day 24	Scotomas gone

Abbreviations: GLP1-RA, glucagon-like peptide-1 receptor agonist; GLP1, glucagon-like peptide 1; OD, right eye; OS, left eye; IZ, interdigitation zone; OCT, optical coherence tomography; RPE, retinal pigment epithelium.

3. Discussion

Here we report a case of an actively practicing cataract/refractive surgery subspecialist who developed a bilateral, incongruous reversible central scotoma observed only under scotopic conditions while taking semaglutide. To our knowledge this is the first case of such symptoms described and expands the knowledge of possible side effects of this new diabetic and weight loss medication. Previous cases of "blurred vision" associated with semaglutide use have been reported in the analysis by the Food and Drug Administration Adverse Event Reporting System (FAERS) from 2018 to 2020, where of 2109 adverse events, 47 cases of blurred vision were reported.[7] Federal reporting systems such as FAERS have various limitations including incomplete reporting, duplicate reports, inaccurate information and unclear causality.[6] One known retinal side effect of semaglutide is the paradoxical worsening of diabetic retinopathy, which is not applicable here as the subject didn't have diabetes or retinopathy.

Although unknown, we postulate the primary location of pathology in our patient may be neurosensory retinal in nature, produced by dysfunction of retinal ganglion cells and their axons. Based on the initial unilaterality of symptoms, a pre-chiasmal location of pathology might be deduced. The central, bilateral location points towards either a macular or optic nerve process. Considering the central scotoma was only present under scotopic conditions, a primary cone pathology is unlikely; if rods were primarily affected, one might expect a more generalized decline. A central scotoma from optic neuropathies is well established and is our leading hypothesis as to where the pathology occurred, but dysfunction involving bipolar cells, photoreceptors or other retinal or vascular cells could be possible.

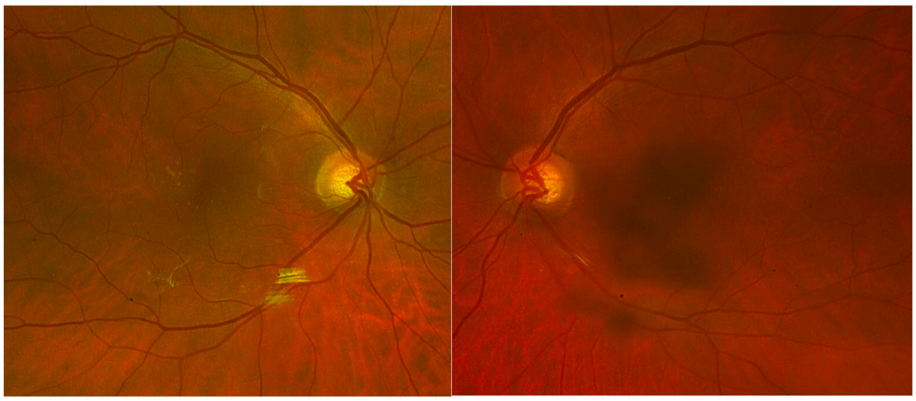

Fig. 3. Optos fundus photography of both eyes demonstrating a mostly benign appearance with a few drusen in both eyes and a PVD in the left eye.

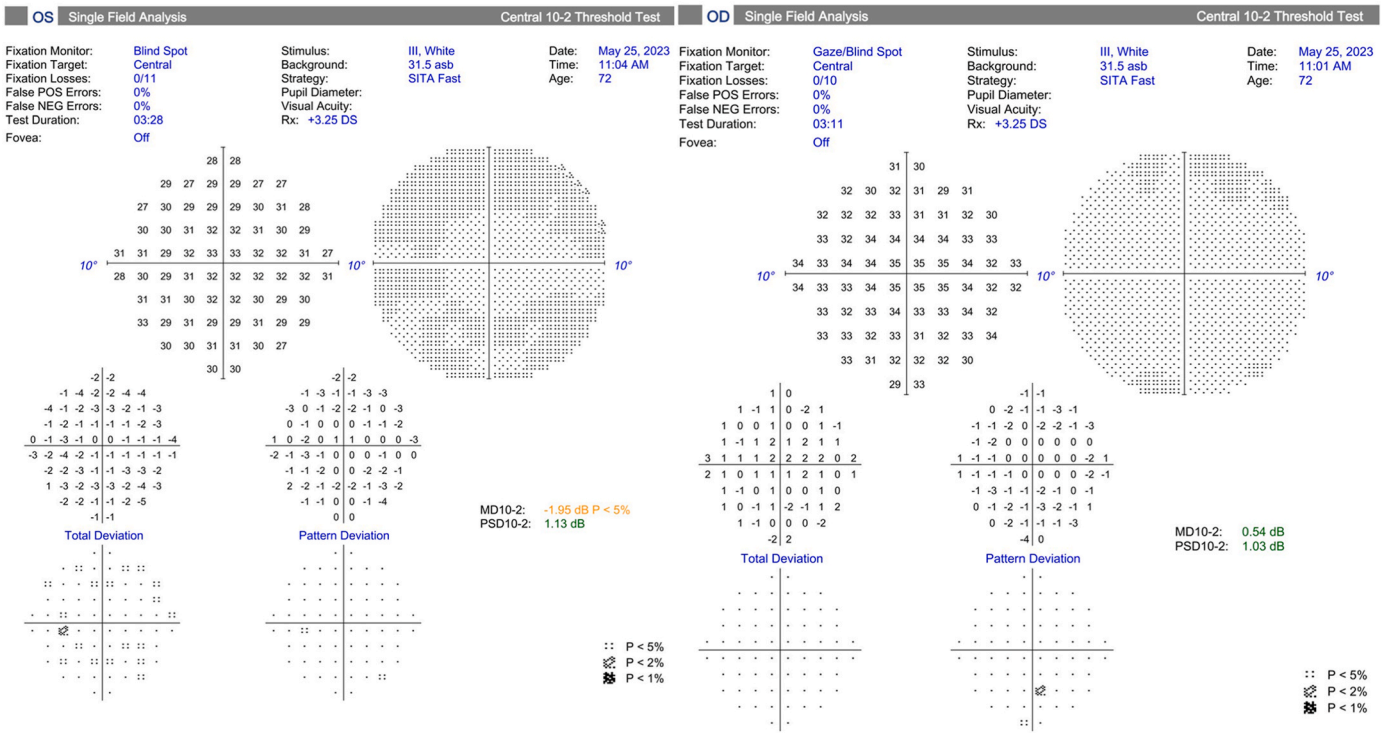

Fig. 4. Humphrey visual fields reveal symmetrically normal highly reliable results for both eyes.

Supporting a possible optic neuropathy is the distribution of glucagon-like peptide-1 receptors in the human retina. While some controversy exists as to the distribution of these receptors,[10] possibly the best evidence localizes GLP1 receptors primarily to the retinal ganglion cells with minimal photoreceptor or RPE expression.[11] Thus, the symptoms experienced and GLP1 receptor distribution are potentially consistent and could provide a possible mechanism for the visual symptoms experienced.

Rybelsus (semaglutide) is a GLP-1R agonist and has a prolonged half-life of 1 week due to a high albumin binding capacity and molecular modifications to avoid enzymatic degradation. It reaches a steady state with daily dosage after 4–5 weeks and has a highest concentration within the body approximately 1 hour after ingestion.[9] The prolonged half-life is possibly consistent with the symptoms persisting for several days following medication discontinuation in this case. The timing of symptoms onset is also potentially consistent with the medication reaching a steady state several weeks after drug initiation.

Medications have often been associated with visual phenomena, though their drug class and categorization of visual symptoms can be broad, making it difficult to ascertain a specific mechanism of symptom production. Perhaps the best intuitively understood would be vasoactive medications impacting cerebral and/or ocular perfusion. These include medications modulating cardiac output and systemic vascular resistance. Beta-blockers, calcium channel blockers, anticholinergics, antihistamines, and medications impacting nitric oxide-dependent processes all have known hemodynamic impact. Vasoactive medications classically cause scintillations which appear to surround visible objects or create a positive starry sky photopsia or a tunneling effect. Other medication-related visual side-effects can occur via progressive optic neuropathy and those with outer retinal toxicity. A classic retinal toxicity medication affecting the macula is hydroxychloroquine, known to be dose dependent and often progressive once observed.[12] These cases can have a variable level of symptomatic and functional impact for patients. Reversible, or partially-reversible, optic neuropathies can be seen with medications such as ethambutol.[13] Amiodarone is another example of a medication associated with optic neuropathy, with variable prognosis once diagnosed. This is hypothesized to be related to its cause of neuronal edema leading to disc edema and compressive loss of axons.[14]

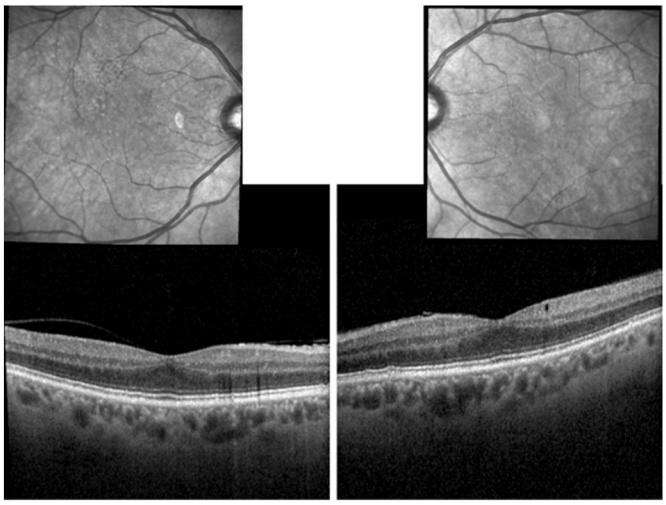

Fig. 5. Macular OCTs demonstrate symmetrically minimal small drusen with normal foveal contours. Mild discontinuity of the interdigitation zone is seen in both eyes, but this is identical to scans taken 8 years before.

Clearly, numerous mechanisms can lead to visual phenomena and these various mechanisms need to be considered when trying to understand any pathophysiology including the one described in this report.

Our case report has limitations. As with all case reports, correlation doesn't necessitate causation and we acknowledge the possibility that these symptoms could be unrelated to semaglutide use. However, in support of causality is the timing of symptoms shortly after drug initiation and resolution of symptoms shortly after drug cessation. Re-initiation of semaglutide treatment was contemplated by our patient to attempt to derive its intended benefit and to see if symptoms might return. But he decided against that out of the concern for the risk of more long-lasting or even permanent vision problems. A comprehensive optic neuropathy workup was not pursued due to the resolution of symptoms following discontinuation of therapy. So, there does exist a possibility that an underlying and unknown issue could have predisposed to the presumed side effect experienced. Finally, testing was only performed after symptoms had resolved, upon return from a vacation. Testing while the patient is symptomatic, with modalities we used in this case as well as possibly fluorescein angiography, OCT angiography, full field and multifocal ERG, and wide-field visual field testing could further elucidate the characteristics of pathology.

Making clinical recommendations based on this one case is challenging. While a decision to stop the medication was made for fear of permanent vision loss, it remains unknown if symptoms would have resolved on their own and we acknowledge the missed benefits of GLP-1R agonists after medication cessation. Since there are alternative treatments for diabetes and weight loss, we are inclined to recommend stopping the medication in similar situations. However, each case requires a personalized approach weighing the pros and cons of treatment modification.

In conclusion, we describe a case of a bilateral, incongruous, reversible central scotoma visible only under scotopic conditions possibly due to oral semaglutide use. Precise symptom description and timing by a board-certified ophthalmologist should increase observation reliability and allow for a better deduction of pathology when clear objective findings were not found. With the popularity of this new medication and mild symptoms, practitioners should be aware of and on the lookout for this possible new association.

Patient consent

Patient consent was obtained for description and publication of this case report.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

CRediT authorship contribution statement

Peter Bracha: Conceptualization, Data curation, Formal analysis, Supervision, Writing – original draft, Writing – review & editing. **William Johnson:** Writing – original draft, Writing – review & editing. **Sabrina Chu:** Writing – original draft. **James Davison:** Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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