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"Optic nerve of steel": A case of very high intraocular pressures with markedly little visual field progression over years

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A B S T R A C T

Purpose: We report a case of pseudoexfoliation glaucoma with exceedingly high intraocular pressures (IOP) but limited visual field progression despite poor adherence with treatment over a 7-year period.

Observation: A 67-year-old Eastern European female presented to the emergency room with an IOP of 52 mmHg OD and exam findings consistent with pseudoexfoliation glaucoma. Subsequent testing demonstrated superior and inferior arcuate deficits on Humphrey visual field (HVF) testing and corresponding thinning of optic nerve OD. The patient was very inconsistent with topical glaucoma medications, and after undergoing selective laser trabeculoplasty she was lost to follow-up without any additional treatment. She returned one year later with an IOP of 59 mmHg, but remarkably stable HVF. The patient refused to restart glaucoma drops and elected instead to proceed with a trabeculectomy OD, which was successfully performed, with the final visual acuity of 20/25 and IOP of 20 mmHg OD. The patient was again lost to follow-up for three years. Her IOP was 40 mmHg OD on return to clinic, but her glaucoma testing revealed very little progression. She decided to pursue placement of glaucoma drainage device (Baerveldt 350) OD, and her IOP was 18 mmHg OD after 6 months on no medications. The patient was lost to follow-up thereafter.

Conclusions: The limited visual field progression with chronically high IOP over years strongly argues in favor of IOP-independent mechanisms contributing to pathophysiology of glaucoma. This case also highlights the importance of longitudinal monitoring and tailoring glaucoma therapy holistically to individual patient circumstances.

1. Introduction

Glaucoma is the leading cause of irreversible blindness, affecting approximately 76 million people worldwide as of 2020.[1] Its histological hallmark is progressive loss of retinal ganglion cells (RGCs), which clinically manifests as optic nerve cupping and visual field (VF) loss. As age is one of the primary risk factors for glaucoma, the number of glaucoma patients is expected to continue to rise, reaching 111.8 million individuals by 2040. Because of the significant morbidity associated with advanced disease, glaucoma poses both a significant public health threat and a serious economic burden.[2]

Elevated intraocular pressure (IOP) is the only modifiable risk factor for glaucoma and is therefore the focus of all existing glaucoma therapies. The currently available treatment options for glaucoma include topical eye drops, selective laser trabeculoplasty (SLT), minimally invasive glaucoma surgery (MIGS) and incisional glaucoma surgery (most commonly trabeculectomy and glaucoma drainage device insertion). However, there are clinical scenarios in which IOP fails to correctly predict disease occurrence and progression. In normal tension glaucoma (NTG), patients with IOPs in the normal range (typically defined as < 21 mmHg) develop progressive optic neuropathy and subsequent VF loss. Although studies have confirmed some effectiveness of IOP-lowering therapies for NTG, the extent of efficacy is insufficient.[3] On the other hand, some patients with IOP moderately above normal range (so-called ocular hypertensives) seem to be protected from optic nerve damage and VF loss and can be often closely monitored without treatment.

Here, we present a case of a patient with pseudoexfoliation glaucoma (PXG) with exceedingly high IOPs and poor adherence with treatment and follow-up visits, who showed remarkably little VF loss over the seven years of follow-up. This case highlights the fact that some individuals can be resistant to even remarkably high IOPs and calls for further investigation into IOP-independent mechanisms contributing to glaucoma pathogenesis.

2. Case presentation

A 67-year-old Eastern European female presented to the emergency

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room with the complaint of blurred vision and pressure sensation over her right eye for three weeks prior to presentation. The patient had no significant eye history. Visual acuity in her right eye (OD) was 20/100, while in the left eye (OS) it was 20/20. IOP measured by Goldmann applanation was 52 mmHg OD and 18 mmHg OS. Slit lamp exam showed pseudoexfoliation (PXF) material on the lens and the iris edge, and mild cataract OD, but was otherwise unremarkable, without evidence of corneal edema. Gonioscopy demonstrated angles open to scleral spur, with significant trabecular meshwork pigmentation noted in the right eye and faint pigmentation in the left eye. Three rounds of pressure-lowering medications and oral acetazolamide were administered, which decreased the pressure to 32 mmHg OD and improved visual acuity to 20/50 OD. Patient was discharged on latanoprost, dorzolamide-timolol, and brimonidine OD, and oral acetazolamide.

Twelve days later on her subsequent follow-up visit in glaucoma clinic, the patient reported intolerance to many of the drops. She consistently took only latanoprost QHS OD but alternated between brimonidine and dorzolamide-timolol daily, and was not taking acetazolamide. Nevertheless, even with this inconsistent regimen her IOP had decreased to 22 mmHg bilaterally. Her central corneal thicknesses were 579 μm OD and 583 μm OS. Fundus exam showed disc cupping and inferior thinning OD (Fig. 1A), without evidence of a central or branch retinal artery or vein occlusion. Optical coherence tomography (OCT) revealed marked thinning of the retinal nerve fiber layer (RNFL) in the right eye and normal RNFL left eye (Fig. 1B). Humphrey visual field (HVF) testing revealed superior and inferior arcuate deficits in the right eye, with mean deviation of −8.70 dB (Fig. 1C). The patient was offered SLT but declined and decided to continue with eyedrops in a more consistent manner. However, on her next follow-up visit two months later, her right eye pressure increased to 35 mmHg in the setting of poor adherence. The patient subsequently underwent SLT OD without complications. On her next follow-up visit one month later, the IOP was 23 mmHg OD and 22 mmHg OS, and her drop adherence was still inconsistent. The importance of medication adherence was emphasized.

Despite the recommended 2-month follow-up interval, the patient was then lost follow-up for more than a year, until she came back with a complaint of blurry vision OD. In the meantime, she had reportedly been seeing a psychic in New York who claimed to have cured her glaucoma; the patient was not taking any glaucoma medications during this time. Her vision OD decreased to 20/100, while her IOP was 59 mmHg OD and 28 OS. However, her OCT and HVF remained remarkably stable compared to her baseline testing, despite remarkably poor IOP control over the past year (Fig. 2A and B). Notably, the decrease in vision the patient noticed was related to the development of a visually significant cataract with myopic shift OD, and not glaucoma progression. The patient declined to start eyedrops again and decided to proceed with combined cataract surgery and trabeculectomy with ExPRESS shunt. The surgery was uneventful and at the end of the postoperative period two months later, patient's vision OD was 20/25 and IOP 20. The patient was adamant about not taking any drops despite the possible risk of progressive vision loss and blindness. The importance of follow-up visits was again emphasized.

Despite the recommended 4-month follow-up interval, the patient was then again lost to follow-up for three years. In the interim her trabeculectomy had scarred down, and her IOP was 40 mmHg OD and 27 mmHg OS on return to clinic, although her VA remained 20/20 bilaterally. HVF testing revealed moderate superior and inferior arcuate defects OD with remarkably little progression given high IOP and lack of monitoring in the interim (Fig. 3). OCT revealed stable thinning of the RNFL OD and normal RNFL thickness OS. The patient restarted eyedrops. On the subsequent visit, the pressure came down to 23 mmHg but she complained greatly about difficulty tolerating the drops, and decided to pursue additional glaucoma surgery. She underwent uneventful placement of a glaucoma drainage device (Baerveldt 350) OD, which decreased her pressure to 18 mmHg 6 months after surgery, with continuing excellent visual acuity of 20/25. Despite a recommended 4-month follow-up interval, the patient was lost to follow-up thereafter. Fig. 3 shows a schematic representation of her IOP measurements, HVFs, surgical interventions and periods of non-adherence over time.

3. Discussion

Elevated IOP is the focus of all existing glaucoma therapies given its positive correlation with visual field progression over time. However, many patients with ocular hypertension (OH) do not develop glaucoma. In the widely cited ocular hypertension treatment study (OHTS), only approximately 9.5 % of patients with OH developed glaucoma after five years, which was reduced to 4.4 % with topical ocular hypotensive medication.[4] The 20-year follow-up of the OHTS subjects revealed that 49.3 % of patients developed glaucoma; however, only 25.2 % of those subjects developed visual field loss.[5] Because only a limited proportion of OH patients ultimately develop loss of vision from glaucoma, many clinicians will observe such patients without treatment after careful considerations of various risk/protective factors.

One such factor is central corneal thickness (CCT). The OHTS study identified that OH patients with CCT of 555 μm or less had a threefold increased risk of developing primary open angle glaucoma within 5 years compared to those with a CCT greater than 588 μm,[6] indicating that thick CCT is a possible protective factor in OH patients. Thick CCT tends to lead to overestimation of IOP measurements by Goldmann and rebound tonometry, but whether there are additional factors that explain why a thick CCT is protective in glaucoma remains unknown. Nonetheless, this set of findings emphasizes the need to perform corneal pachymetry in all patients being evaluated for glaucoma. To aid clinical decision making, a number of useful tools, including the OHTS prediction model[10] and Laroche glaucoma calculator,[11] have been developed. Notably, these tools have been validated for OH patients, whereas the predictive role of CCT to the prognosis of glaucoma with existing optic nerve damage has not been well-established.[9]

Our patient had CCTs of 579 μm OD and 583 μm OS, while the average CCT is around 536 μm with an standard deviation (SD) of 31 μm.[7] For patients of Russian ancestry like our patient, average CCT is around 549.5 μm with SD being 32.8 μm.[8] Thus, while our patient did have a moderately thick CCT – within 2 SDs above the population average and 1 SD above the Russian average – this may not fully explain our patient's extraordinary protection from the exceptionally high IOP in the setting of PXF glaucoma. While visual field protection from moderately high IOP was revealed in the OHTS, it is important to emphasize that the IOP range of participants recruited in this study was between 21 and 32 mmHg, much lower than our patient's IOP of 59 mmHg. A comprehensive literature review performed on 11/14/2024 using PubMed of over 700 case reports using terms "high IOP visual field", "ocular hypertension visual field," and "severe ocular hypertension visual field" yielded no similar cases of exceedingly high IOP without significant visual field progression.

The fact that this patient's optic nerve was protected from exceedingly high IOP over extended periods of time demonstrates that there must exist IOP-independent mechanisms that can either predispose patients to glaucoma (as is the case in NTG) or conversely protect them from damage in the cases of higher-than-normal IOP. One possible approach to deciphering these additional mechanisms takes advantage of human genetic studies, which have revealed association of numerous genes, including LTBP2, CYP1B1, PAX6, and optineurin as well as 312 additional loci with glaucoma.[12–17] Interestingly, a genetic follow-up study of the OHTS participants identified TMCO1, an endoplasmic reticulum (ER) calcium-selective channel in response to ER calcium overloading, as a risk gene for non-Hispanic white descendants, wherein patients with the risk *TMCO1* allele had a 12 % higher cumulative incidence of developing glaucoma compared to those with non-risk allele. Further additional studies revealed that the length of *TMCO1* tandem repeat is inversely correlated with the age of onset of primary open angle glaucoma (POAG).[4,18,19]

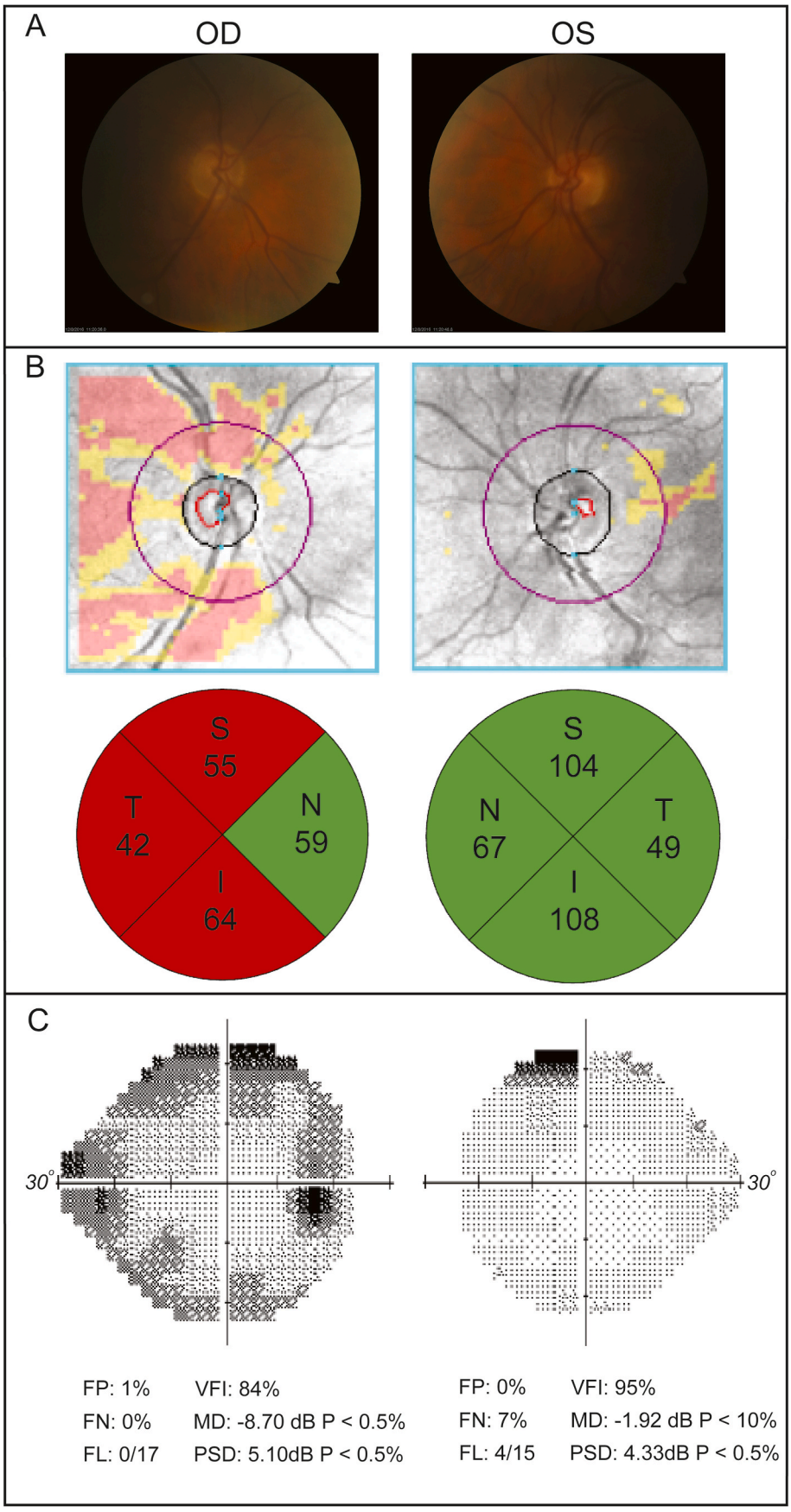

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Fig. 1. Baseline glaucoma testing at the first clinic visit. A). Optic disc photos reveal cupping of the right optic nerve and normal left optic nerve. **B).** Optical coherence tomography results show superior, inferior and temporal thinning of the right optic nerve (average thickness 55 μm) and normal left optic nerve (average RNFL thickness 82 μm). **C).** Humphrey visual field testing shows early superior and inferior arcuate OD (MD = −8.70 dB) and reassuring left visual field with mild lid artifact.

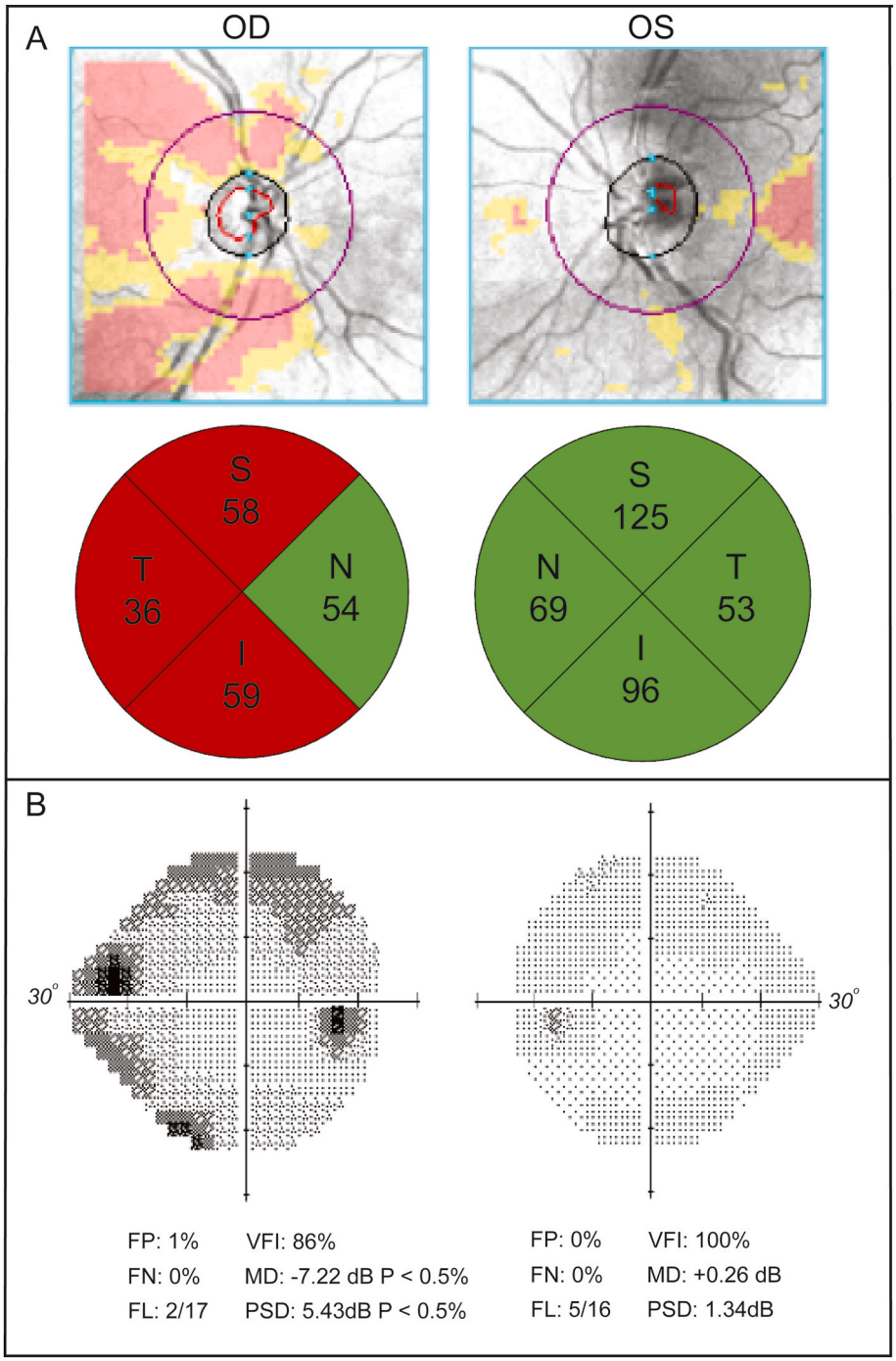

Fig. 2. Glaucoma testing one year after the initial visit, after patient's first loss to follow-up. A). Optical coherence tomography results show stable thinning of the right optic nerve and normal left optic nerve (average RNFL thickness: 51 μm OD, 86 μm OS). **B).** Humphrey visual field results show mild superior and inferior arcuate field deficits with remarkably little progression since the first visit in the right eye (MD = −7.22), and normal visual field in the left eye.

In addition, numerous basic science studies have demonstrated presence of IOP-independent mechanisms for glaucoma in animal models. Many studies have described cell-autonomous mechanisms rendering RGCs susceptible to glaucomatous neurodegeneration. For example, deprivation of neurotrophic factors is thought to contribute to neurodegeneration in glaucoma, while supplementation with neurotrophic factors, such as brain-derived neurotrophic factor, ciliary neurotrophic factor, and glial cell line-derived neurotrophic factor, was shown to be effective in reducing RGC loss in experimental glaucoma.[20,21] Meanwhile, metabolic vulnerability in glaucoma has also

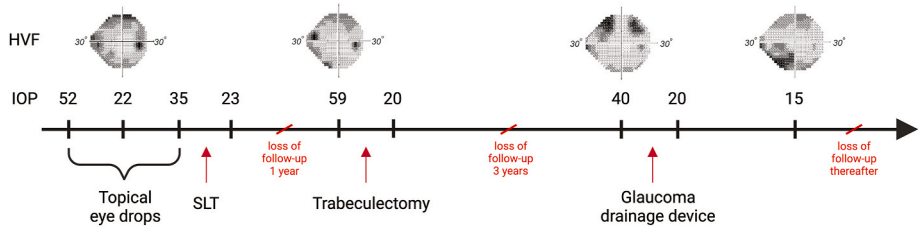

Fig. 3. Glaucoma progression timeline. The schematic shows the intraocular pressure (IOP) and Humphrey visual field (HVF) findings at different time points in the case history. The key treatments (medications, SLT and surgeries) provided to the patient are listed on the bottom.

been extensively studied, and revealed vitamin B3 (nicotinamide) supplementation as a promising neuroprotective treatment to prevent glaucoma in both experimental glaucoma models and early human studies.[22–25]

Chronic neuroinflammation has also been shown to critically contribute to pathogenesis of glaucoma. For example, recent studies investigating the role of immune mechanisms of glaucoma demonstrated that infiltrating T cells against heat-shock proteins (HSP) contributed to the progressive, IOP-independent phase of glaucomatous degeneration in the microbead glaucoma model. Compared to healthy controls, POAG patients also exhibited increased frequency of HSP-specific type 1 $CD4^+$ helper T cells, which was negatively correlated with RNFL thickness.[26] Furthermore, $CD4^+$ T cell isolated from glaucoma patients also appeared to be in a more activated state, and the increased activation positively correlated with visual impairment and negatively correlated with RNFL thickness.[27]

Microglia, the resident immune cells of the central nervous system, have also been implicated in glaucoma pathogenesis through many studies.[28] A recent study from our laboratory demonstrated that microglia in glaucoma switch from the homeostatic to a disease-associated state (DAM), which is also seen in brain neurodegenerative diseases such as Alzheimer's disease, multiple sclerosis, and amyotrophic lateral sclerosis.[29,30] DAM microglia produce high levels of molecules Apolipoprotein E (APOE) and Galectin-3, whose genetic and pharmacologic targeting protected RGCs from death despite elevated IOP in the microbead mouse model of glaucoma. Interestingly, mice with *APOE4* allele, a genetic variant of *APOE* that is a well-established risk factor for Alzheimer's disease, were also protected from RGC loss in the mouse model, and the same allele was associated with a decreased risk of human glaucoma.[15,30,31] While our patient's genetic make-up is unknown, it is tempting to speculate that she may harbor protective allele(s) that are dramatically decreasing her rate of glaucomatous progression despite IOPs that would lead to catastrophic vision loss in most other patients.

4. Conclusion

Although IOP is currently the only modifiable risk factor for glaucoma and the target of all existing glaucoma therapies, our case highlights the fact that it is not always an accurate predictor of visual field progression. Given that some patients may have progressive glaucoma even with IOP in normal range, and others seem to be resistant to elevated IOPs, it is important to carefully follow patients over time and develop a holistic treatment plan that considers patient's disease trajectory, lifestyle, ability to adhere to medications and visit schedule, and ocular and systemic co-morbidities. In addition, the extraordinary protection that our patient demonstrated despite extremely elevated IOPs over the period of years strongly suggests that pathogenic mechanisms independent of IOP contribute to glaucoma, arguing in favor of more basic science research into the pathophysiology of this common blinding disease.

CRediT authorship contribution statement

Yixi Xue: Writing – original draft, Visualization. **Milica A. Margeta:** Writing – review & editing, Validation, Conceptualization.

5. Patient consent

Consent to publish all information related to this case was obtained from the patient.

Authorship

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

Claim of priority

A comprehensive literature review performed on 11/14/2024 using PubMed of over 700 case reports using terms "high IOP visual field", "ocular hypertension visual field," and "severe ocular hypertension visual field" yielded no similar cases of exceedingly high IOP without significant visual field progression.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, none of the authors used any generative AI or AI-assisted technologies in any way.

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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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