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Intracranial hypertension associated with topical tretinoin use

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ABSTRACT

Purpose: To report cross-reactivity between topical vitamin A derivatives and tetracycline-class antibiotics.
Observations: A 19-year old woman with a remote history of resolved secondary intracranial hypertension due to minocycline use developed intracranial hypertension while using topical tretinoin alone. Examination demonstrated bilateral optic nerve edema, a right sixth cranial nerve palsy, along with characteristic features of markedly elevated intracranial pressure on imaging. Lumbar puncture opening pressure was 60 cmH_2O. Cessation of topical tretinoin use ensued complete resolution of symptoms and optic nerve swelling in both eyes.
Conclusions and importance: Our findings substantiate the need to avoid topical vitamin A derivatives and alternate drug classes known to be associated with drug-induced intracranial hypertension.

1. Introduction

Vitamin A derivatives and tetracycline-class antibiotics are among known medications associated with drug-induced intracranial hypertension (DIIH). Presenting symptoms including headaches, transient visual obscurations, and compressive optic neuropathy leading to irreversible severe visual impairment are well-documented.[1] There remains a paucity of data regarding topical tretinoin and its association with secondary intracranial hypertension. Thought to be a safer option than systemic isotretinoin, topical tretinoin, or all-trans-retinoic acid, is an active intracellular metabolite of isotretinoin (13-*cis*-retinoic acid) often prescribed as a first-line treatment for patients with mild-to-moderate acne vulgaris.[2] There have been two previous reports of topical formulations of vitamin A linked to intracranial hypertension.[3,4] However, to the best of our knowledge, there have been no reported cases of cross-reactivity with topical tretinoin use and alternate drug classes associated with DIIH. We report the first case of secondary intracranial hypertension associated with topical tretinoin in a patient with a remote history of tetracycline-induced intracranial hypertension.

2. Case

A 19-year old woman (BMI of 31.1) with a remote history of secondary intracranial hypertension due to minocycline use presented with headaches and worsening vision. Three years after minocycline cessation and confirmed resolution of elevated intracranial pressure, the patient was started on topical tretinoin. One year later, she developed headaches, nausea, visual obscurations, and a right sixth cranial nerve palsy. Fundus examination revealed bilateral optic nerve edema (Fig. 1A). MRI of the brain and orbits demonstrated characteristic features of markedly elevated intracranial pressure (Fig. 2A and B). MRV of the brain demonstrated severe transverse sinus stenosis without occlusion (Fig. 2C). Lumbar puncture (LP) opening pressure was 60 cmH_2O with normal cerebrospinal fluid (CSF) composition. She underwent unilateral transverse sinus stenting, and was monitored closely on an outpatient basis with strong emphasis placed on complete cessation of topical tretinoin use. Humphrey visual field (HVF) 24–2 testing demonstrated significant visual field defects bilaterally upon presentation (Fig. 3A). After topical tretinoin cessation and cerebral venous sinus stenting, symptoms along with optic nerve edema completely resolved (Fig. 1B) and visual field defects continued to improve (Fig. 3B).

3. Discussion

Secondary intracranial hypertension is a potential adverse effect of certain medication classes. A recent systematic review proposed a set of diagnostic criteria for DIIH, elucidating that vitamin A derivatives and tetracycline-class antibiotics are among the highest-risk category.[1] They are both category V medications (medications found to be most strongly associated with DIIH)[1] and may even have a synergistic effect on

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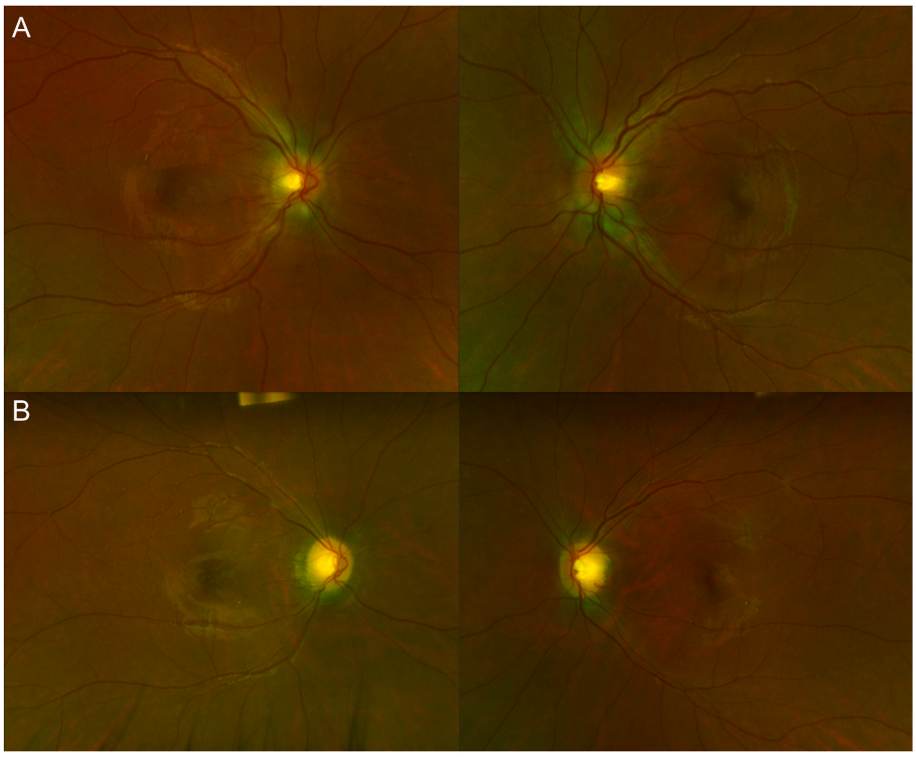

Fig. 1. Optos fundus photographs (Optos, Marlborough, MA) demonstrating optic nerve edema with subsequent resolution in both eyes after complete cessation of topical tretinoin use. **(A)** Optic nerve edema upon presentation while using topical tretinoin. **(B)** Resolution of optic nerve edema 6 months after cessation of topical tretinoin.

inducing DIIH.[6] Studies have demonstrated that tetracyclines should not be prescribed concurrently with isotretinoin, and a drug-free period of at least seven days is recommended to achieve theoretical drug clearance.[2,9,10] Despite these recommendations, cases of drug-induced intracranial hypertension preceded by concomitant use of tetracycline and isotretinoin exist.

Although topical formulations of vitamin A have rarely been linked to intracranial hypertension,[3,4] its relationship with alternate drug classes has never been reported. Additionally, while it is rare for topical tretinoin to have substantial systemic absorption and subsequently have adverse systemic effects, this must always be a consideration. Our patient had a remote, resolved history of DIIH secondary to minocycline use and developed intracranial hypertension whilst using topical tretinoin only, many years later. Because there are only a couple of reported cases of DIIH with topical vitamin A derivatives, patients with secondary intracranial hypertension have been prescribed such medications from alternate drug classes. The exact mechanism by which tretinoin and tetracycline-class antibiotic induce intracranial hypertension is unclear. Current hypotheses include that tetracyclines may impede CSF outflow at the arachnoid villi while oral retinoids may be directly toxic to arachnoid villi function.[5,6] Our case report is in stark contrast to the proposal that patients who have suffered DIIH with one class of medication can safely be treated with alternate medication classes.[5,7,8] We highlight the need to carefully consider use of medications known to cause DIIH in patients who have experienced DIIH in the past. Based on our findings, alternate classes of drugs that are independently known to cause IIH should be approached with caution and vigilant surveillance, as there may be a similar undiscovered mechanism of causation.

The results of our report not only substantiate the need to avoid use of alternate drug classes known to cause DIIH in those with a history of intracranial hypertension, but also demonstrate a potential cross-reactivity between two classes of drugs that needs to be further elucidated. Our findings will assist physicians with proper counseling and decision-making when prescribing such medications. To improve patient safety and decrease the risk of potentially irreversible vision loss, patients taking these medications should receive routine ophthalmologic examination.

Patient consent

Consent to publish this case report was not obtained as this report does not contain any identifiable personal information.

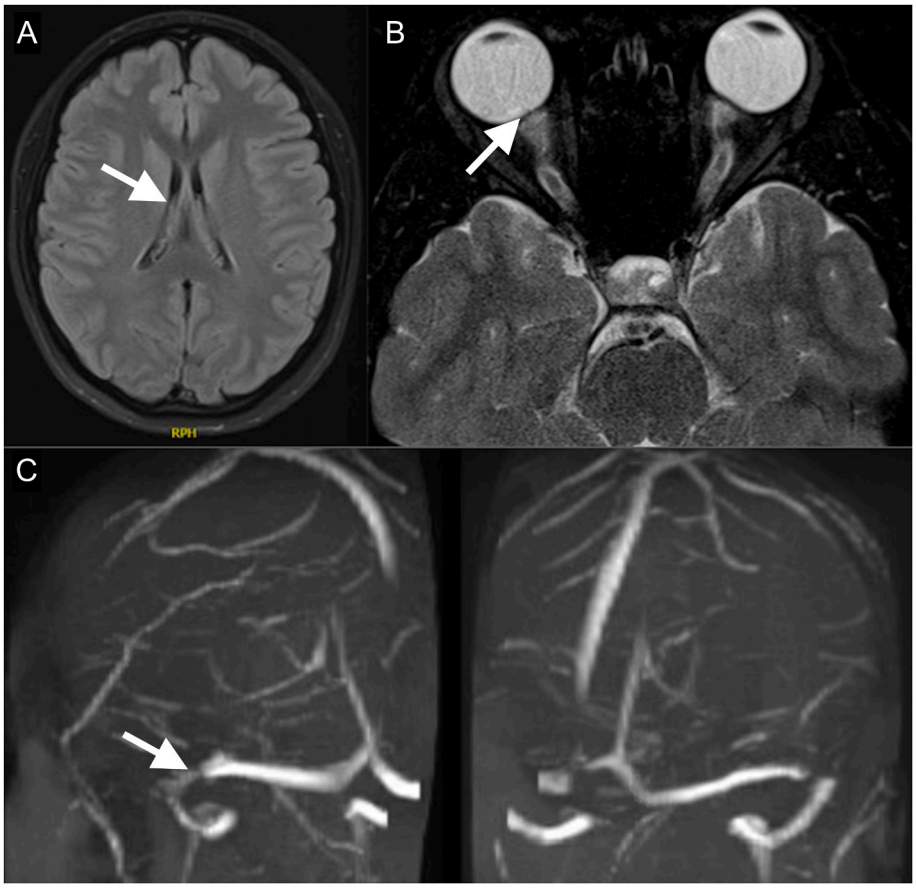

Fig. 2. MRI/MRV of the brain and orbits demonstrating characteristic features of elevated intracranial pressure. **(A)** MRI of the brain demonstrating slit-like ventricles bilaterally. **(B)** MRI of the orbits demonstrating flattening of posterior globes. **(C)** MRV of the brain demonstrating bilateral transverse sinus stenosis without thrombosis.

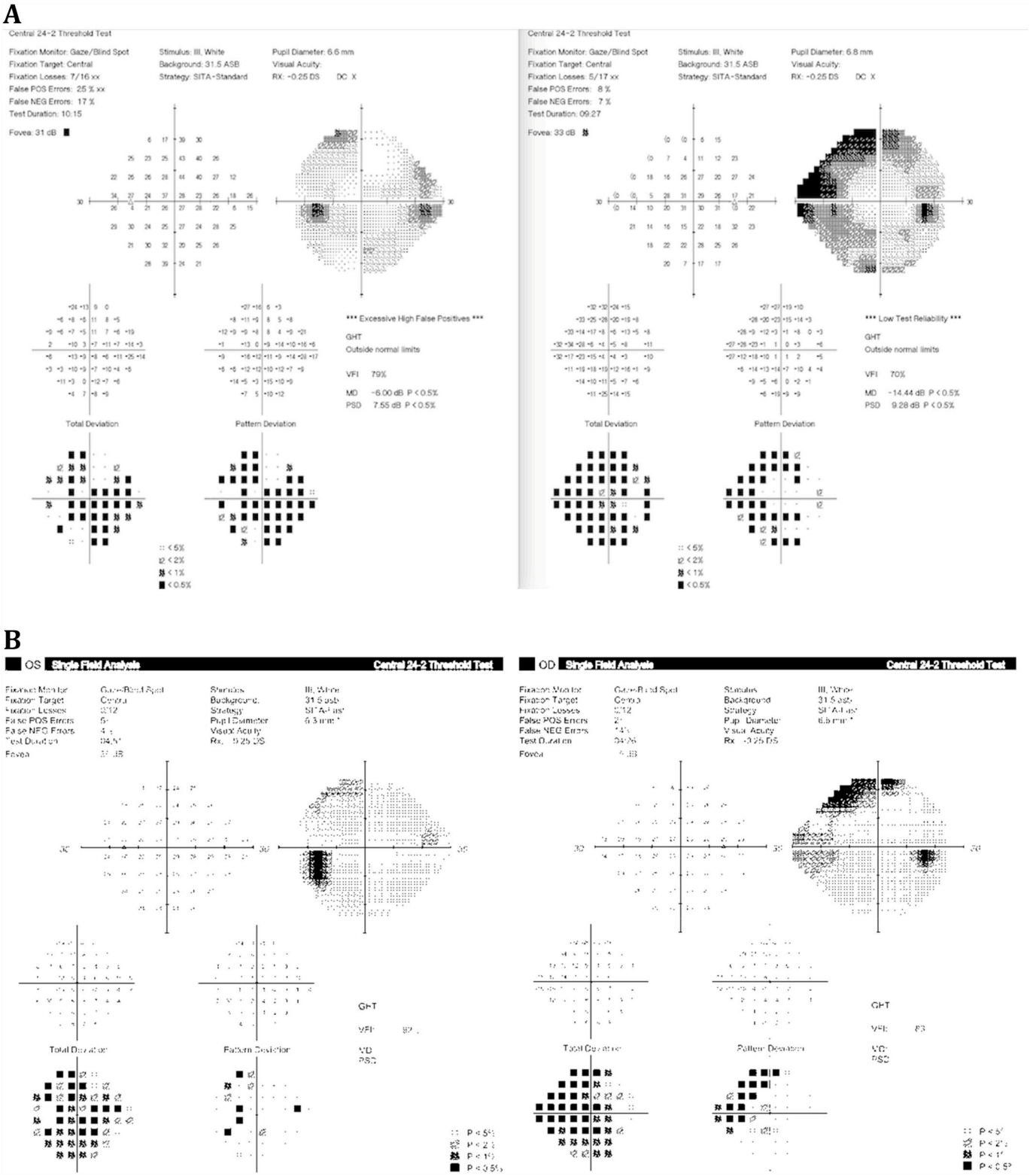

Fig. 3. Humphrey Visual Field (HVF) 24–2 testing demonstrating improvement in visual fields over the course of 1 year after topical tretinoin cessation. **(A)** HVF 24–2 visual field defects in both eyes in the setting of topical tretinoin use. **(B)** HVF 24–2 findings 1 year after topical tretinoin cessation.

Authorship

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

Declaration of competing interest

The following authors have no financial disclosures: SG, XG, EH.

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