LETTER TO THE EDITOR

To The Editor

Rapid Development of Optic Disc Edema Secondary to Topical Retinoid Cream

Keywords: Secondary intracranial hypertension, Retinoic acid, Minocycline

We described a case of a young woman with remote history of intracranial hypertension secondary to tetracycline use who developed optic disc edema 1 week after starting treatment with a topical retinoic acid. This case highlights the fact that predisposed individuals with previous history of medication-induced intracranial hypertension can have exquisite sensitivity to even topical agents containing retinoic acid and can develop optic disc edema quickly when re-challenged with another agent known to cause intracranial hypertension.

A 19-year-old woman was seen in routine follow-up for history of bilateral optic neuropathy secondary to the use of oral tetracycline for acne over 5 years ago. At the age of 14, she developed severe headaches and nausea 1 month after starting therapy with tetracycline for acne. She was eventually found to have bilateral optic nerve head edema. MRI of the brain at that time revealed bilateral narrowing of the transverse-sigmoid junction with partial empty sella, and lumbar puncture demonstrated elevated opening pressure but had normal composition. A diagnosis of tetracycline-induced increased intracranial pressure (ICP) was made, the offending medication was stopped, and, after a short course of treatment with acetazolamide and topiramate, her symptoms resolved. Papilledema also gradually resolved and her visual function remained normal, although she was left with residual left optic nerve head pallor.

When assessed by our service, she had been off acetazolamide and topiramate for over 3 years and was asymptomatic. Her body mass index was 24.9. Visual acuity was 20/20 in the right eye and 20/25 in the left eye (LE) with left relative afferent pupillary defect (RAPD). Right optic nerve was pink, while the left optic nerve was diffusely pale, ocular coherence tomography (OCT) of both the peripapillary retinal nerve fiber layer (RNFL) and macular ganglion cell complex demonstrated bilateral thinning, greater on the left and visual fields showed minimal inferior nerve fiber bundle defect in LE (Figure 1A). An examination was unchanged from previous, and the patient was asked to follow up with her optometrist in 1 year.

Six weeks later, however, she presented to her local emergency department with a 1-week history of severe headaches. She was noticed to have bilateral optic disc edema and was seen by our service again 3 days later. Central acuity was

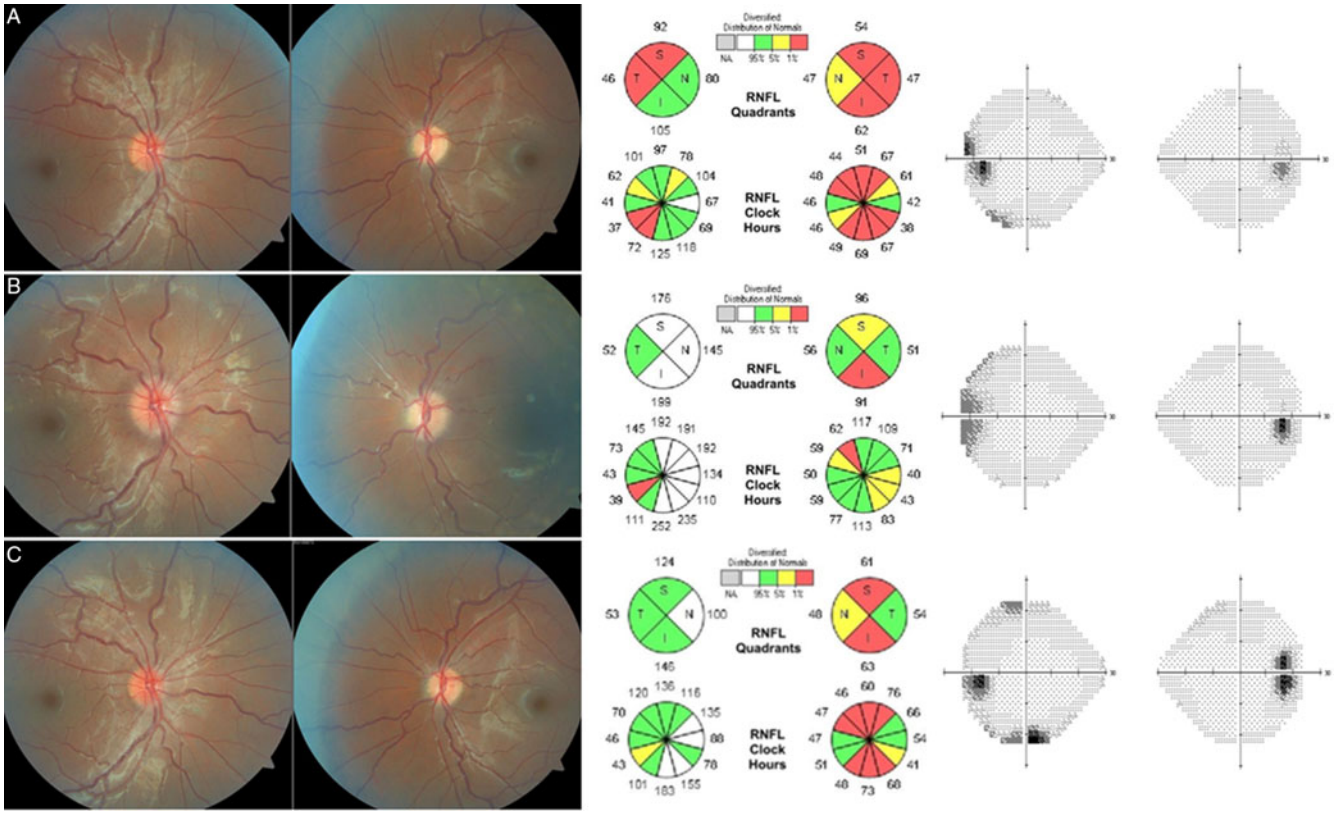

Figure 1: *Papilledema secondary to topical tretinoin. (A) Baseline posterior pole photos showing left optic disc pallor with retinal nerve fiber layer (RNFL) thinning and minimal visual fields changes in the left eye on peripapillary ocular coherence tomography (OCT). (B) Shortly after starting topical tretinoin containing medication, bilateral optic disc edema is now present in each eye with RNFL thickening on peripapillary OCT. (C) After tretinoin discontinuation, optic disc edema resolved completely with decrease of peripapillary RNFL thickness on OCT.*

https://doi.org/10.1017/cjn.2021.11 Published online by Cambridge University Press

still 20/20 in each eye with left RAPD. She now demonstrated an obvious swelling of the right optic nerve and mild elevation of the atrophic left optic nerve on ophthalmoscopy which was confirmed with peripapillary OCT demonstrating significantly elevated RNFL thickness compared to the previous assessment 1 month ago (average RNFL thickness was 143 and 74 µm compared to 81 and 52 µm previously) (Figure 1B). When questioned about any changes in her medication history, she revealed that she started a new topical cream containing tretinoin 0.025% 2 weeks ago, with approximately 10 applications. Repeat MRI and MR venogram showed indirect signs of raised ICP but was otherwise normal. When she was asked to stop using this cream immediately and reassessed 1 month later, previously seen optic nerve head edema had resolved on ophthalmoscopy which was also confirmed on peripapillary OCT measurements (Figure 1C).

This patient with a history of medication-induced increased ICP secondary to tetracycline demonstrated an exquisite sensitivity to tretinoin, with optic disc edema developing within 2 weeks of starting a low-dose skin cream containing this medication. The first report of tretinoin-induced papilledema was in pediatric patients taking an oral formulation between 50 and 90 mg daily for treatment of acute promyelocytic leukemia, with onset as early as 1 week after initiation.[1] Topical tretinoin has been reported to produce intracranial hypertension when taken concurrently with oral doxycycline for 2 months[2] but not as a single agent. There are rare reports of other topical retinoids at higher doses causing papilledema over many weeks.[3]

Of the drugs reported to be associated with intracranial hypertension, the strongest links have been made to tetracyclines and vitamin A derivatives such as isotretinoin and tretinoin. This observation led to the speculation that tetracyclines produce their effect on ICP through activation of retinoic acid receptors (RARs) within the brain. The mechanism through which retinoids produce elevated ICP is unclear but may involve regulation of CSF dynamics. Activation of RARs can decrease permeability of neurovascular endothelial cells through induction of cadherin expression[4] and may result in decreased CSF absorption through arachnoid granulations. Tetracyclines have also been reported to alter endothelial cell function and preserve the integrity of the blood–brain barrier in animal models.[5] It is not known whether this effect involves RAR signaling pathways; however, anti-inflammatory effects of minocycline have been shown to require retinoids in vitro.[6] We suggest that upregulation or sensitization of RARs may occur after exposure to tetracyclines in susceptible individuals and create a dramatic response to even low-dose vitamin A derivatives. Notably, elevated ICP has been reported weeks after tetracycline discontinuation, which supports the idea that effects of this medication may be long-lasting.[7]

This case emphasizes that vitamin A derivatives known to produce increased ICP can also be the culprit when used as a topical preparation. It also demonstrates that individuals with history of tetracycline-induced increased ICP can show increased sensitivity to retinoid derivatives and can develop optic disc edema after a low-dose exposure to the offending agent and should be carefully observed when exposed to any other agents known to produce drug-induced intracranial hypertension.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Statement of Authorship

LD and EM wrote the manuscript and approved the final version.

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https://doi.org/10.1017/cjn.2021.11 Published online by Cambridge University Press