Toxic Optic Neuropathy: A Rare but Serious Side Effect of Chloramphenicol and Ciprofloxacin

Sir,

Toxic optic neuropathy (TON) is an optic nerve dysfunction resulting from exposure to toxin and is characterized by painless, progressive, bilaterally symmetrical visual impairment along with color vision abnormality. It is usually associated with central or centrocecal scotomas due to papillomacular bundle damage.\textsuperscript{[1,2]} The impaired color perception may be selective (particularly red) or generalized and is often disproportionate to vision loss.\textsuperscript{[2]} We describe a case of bilateral TON that developed in the setting of prolonged use of chloramphenicol and ciprofloxacin.

A 30-year-old gentleman presented with 1-week history of progressive, painless loss of vision in both eyes; right > left. He complained difficulty in reading and appreciating colors. There was no history of redness of eyes, ptosis or double vision, fever, headache, or vomiting. Following fracture at left ankle, he developed chronic osteomyelitis for the past 3 months and was prescribed ciprofloxacin 750 mg per orally (p.o.) once daily (OD) and chloramphenicol 2 g p.o. OD, which he continued since then. The patient was an office clerk by occupation and had a nonvegetarian dietary habit. There was no other significant medical or family history or history of any substance abuse. He was a nonsmoker and nonalcoholic.

Clinical examination on day 8 of illness revealed best-corrected visual acuity (BCVA) of 6/18 in the right eye and 6/12 in the left eye. Pupil examination was unremarkable with no relative...
affection pupillary defect. There was significant reduction in generalized color perception in both eyes (right > left) when tested with Ishihara’s color plates. Fundus examination revealed bilateral mild blurring of disc margins and mild tortuosity of retinal vessels at posterior pole. The left eye additionally showed small superficial retinal hemorrhage along inferior arcade [Figure 1a and b]. Humphrey visual field testing showed bilateral centrocecal scotoma [Figure 1i]. Remainder of the cranial nerves and neurological examination including motor, sensory, and cerebellar system examination was unremarkable.

Laboratory work-up including complete blood count and red blood cell indices, inflammatory markers, folic acid and vitamin B12 levels, blood glucose along with HbA1c, renal and liver function tests, and thyroid profile were found normal. Fundus fluorescein angiography revealed no significant abnormality except a small area of block fluorescence corresponding to an area of retinal hemorrhage in the left eye [Figure 1c-f]. Visual evoked potentials (VEP) showed prolonged P 100 latency bilaterally. Optical coherence tomography (OCT) revealed increased retinal nerve fiber layer (RNFL) thickness [Figure 1k] which corresponds to disc edema in fundus photograph [Figure 1a and b] and can be attributed to RNFL edema in acute stage. Contrast-enhanced magnetic resonance imaging of the brain including orbit, cerebrospinal fluid analysis including IgG index and oligoclonal bands, and nerve conduction studies were unremarkable.

Based on the characteristic clinical picture of bilateral painless progressive vision loss along with generalized color vision defect and bilateral centrocecal scotoma on visual field examination along with lack of any significant biochemical or neuroimaging abnormality, possibility of TON secondary to chloramphenicol and ciprofloxacin was the primary differential considered. A normal neuroimaging and unremarkable cerebrospinal fluid examination reduced the likelihood of a demyelinating optic neuropathy. In view of the available clinical and investigational findings favoring TON, a hereditary mitochondrial pathology was less likely.

Unremarkable neuroimaging also ruled out the possibility of compressive or infiltrative lesions involving optic nerve or optic chiasma. Normal serum B12 level ruled out optic neuropathy resulting from its deficiency.

Considering the primary possibility of TON secondary to chloramphenicol and ciprofloxacin, both these drugs were stopped immediately. High doses of B vitamins including B12 1000 µg p.o. OD, B6 100 mg p.o. OD, and folic acid 5 mg p.o. OD were prescribed. His visual acuity and color perception started improving over the next 3–5 days, and 2 weeks after stopping the offending drugs his BCVA was 6/12 in the right eye and 6/9 in the left eye. Three months after stopping chloramphenicol and ciprofloxacin, visual acuity improved to 6/6 bilaterally with normal color vision. Fundus examination revealed mild temporal pallor of bilateral discs with well-defined margins [Figure 1g and h]. Visual field examination [Figure 1j] and VEP also normalized at 3 months follow-up. OCT at 3 months of follow-up showed normalization in RNFL thickness in almost all quadrants in both eyes [Figure 1l].

Optic neuropathy can result from various causes including vascular, inflammatory, nutritional, toxin, and hereditary. The clinical features of nutritional and TON are very similar. Therefore, nutritional causes must be excluded before a diagnosis of TON is made. TON can result from a number of drugs and toxins and is dose- and duration-dependent [Table 1]. The characteristic clinical presentation, lack of nutritional deficiency, and complete improvement after stopping the offending drugs established the diagnosis of TON in our patient. In the early stages of TON, the optic nerves may appear normal. Papillomacular bundle loss and optic atrophy develop at variable intervals from the disease onset depending on the toxin responsible. VEP may show increased latency in cases of TON.

Toxins usually impair tissue’s metabolism or vascular supply. Although distinctive configuration of vascular supply of optic nerve head predisposing to accumulation of toxic substance has been hypothesized, the cause for selective damage of papillomacular bundle remains unclear. TON due to chloramphenicol, first reported in 1950s, is both duration- and dose-dependent. It has been hypothesized that chloramphenicol inhibits vitamin B12 metabolism rather than directly reducing its serum levels. In our patient, vitamin B12 levels were normal. The mechanism of ciprofloxacin-induced optic neuropathy also remains unknown and the role of common quinolone group as a toxic agent has been hypothesized. In fact, TON may be considered as acquired mitochondrial optic neuropathies.

A complete recovery in visual acuity has been reported in half of the patients if offending drug is withdrawn timely and high dosage of vitamin B6 and B12 is administered systemically, suggesting reversible nature of the disease in initial stage. It has also been reported that high daily doses of B vitamins (pyridoxin and cyanocobalamin) in patients taking chloramphenicol may prevent TON.

### Table 1: Common causes of toxic optic neuropathy (modified from Grazybowski et al.[1] and Sharma and Sharma[2])

| Drugs and toxin groups | Agents causing toxic optic neuropathy |
|-----------------------|--------------------------------------|
| 1. Antibiotics         | Chloramphenicol, ciprofloxacin, linezolid, sulfonamides |
| 2. Antitubercular drugs | Ethambutol, isoniazid |
| 3. Antimalarials       | Chloroquine, quinine |
| 4. Chemotherapeutic agents | Vincristine, methotrexate, cisplatin, carboplatin |
| 5. Antiarrhythmics     | Amiodarone, digitalis |
| 6. Antiepileptics      | Vigabatrin |
| 7. Alcohols            | Methanol, ethylene glycol |
| 8. Heavy metals        | Lead, mercury, lithium |
| 9. Miscellaneous agents | Carbon monoxide, tobacco |
Our case highlights a rare but serious complication of commonly used antibiotics as chloramphenicol and ciprofloxacin. It emphasizes the importance of baseline evaluation of visual functions before initiating these antibiotics especially when planning to continue at higher doses and for a prolonged period. In addition to the periodic evaluation of visual functions every 3 months, such patients should be educated to immediately report any visual symptom. Prompt cessation of the offending drugs is the key in managing such cases.

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Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given his consent for images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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