Metronidazole-Induced Irreversible Optic Neuropathy

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Abstract
Metronidazole-induced optic neuropathy is a rare complication. Most patients have excellent visual recovery. In this study, we report a patient who presented with a sudden onset of severe visual loss after a 1-week course of metronidazole. Myelitis developed simultaneously. The vision and the accompanying neurological deficiency of the patient did not improve even after metronidazole was discontinued immediately and various treatments were given.

Introduction
Metronidazole has been a commonly used as an anti-anaerobic agent for treating bacterial and protozoan infection for decades. However, the association of metronidazole with neurotoxicity, including optic neuropathy, has been reported [1]. Fortunately, visual impairment is reversible after cessation of the drug [2]. Herein, we report a patient who experienced irreversible and severe visual loss after metronidazole treatment.

Case Report/Case Presentation
A 57-year-old woman with underlying diseases, including coronary artery disease, ESRD under regular hemodialysis, and dyslipidemia, had been taking metronidazole for 1 week for vaginitis (1,000 mg/day). She started experiencing unstable gait with ataxia, bilateral upper limb tremor, and general myoclonus associated with blurred vision. She was admitted to the neurology ward and an ophthalmologist was consulted. She denied a history of trauma, insect bites, vaccinations, travel, and exposure to toxic chemicals. She has no family
history of blindness, either. Upon examination, visual acuity was hand motion in both eyes with sluggish pupillary reaction. The results from ocular motility, intraocular pressures, external eye exam, funduscopic examination, and optical coherence tomography were normal. Because her vision was very poor, visual field examination could not be performed. The visual evoked potential test showed an absence of waveform in both eyes. Her chest radiograph was normal, and brain MRI with angiography and venography was unremarkable, either. The spine MRI showed a hyperintense lesion at T1–T2 level of the spinal cord. Axonal damage was noted in nerve conduction studies. Cerebrospinal fluid examination showed an elevated protein level.

Routine blood cell counts were within the normal range, except for an elevated erythrocyte sediment rate (25 mm/h). The immunological profile (antinuclear antibody, anti-double-stranded DNA, anti-extractable nuclear antigen, and anti-neutrophil cytoplasmic antibody, rheumatoid factor, C3, and C4), serological tests for syphilis (rapid plasma test and Treponema pallidum particle agglutination assay), and antibody tests for cytomegalovirus and toxoplasma were normal. Results from nutritional screening (serum zinc, vitamin B12, folate, and iron) were normal. Aquaporin-4 and myelin oligodendrocyte glycoprotein antibodies were negative.

Metronidazole was stopped immediately after metronidazole-induced optic neuropathy and myelitis were detected; however, the patient reported numbness and weakness in the limbs a few days after admission. Pulse therapy was used for 5 days; thereafter, oral prednisolone 50 mg/day (body weight 42 kg) was administered. Due to abdominal discomfort, the steroid was tapered. However, her vision worsened to light perception in both eyes and she was given plasmapheresis therapy. After 5 sessions of plasmapheresis, her vision remained the same. Therefore, intravenous immunoglobulin was administered to the patient. However, her vision did not improve after this treatment.

Discussion/Conclusion

Metronidazole, a nitroimidazole, is an antibacterial and antiprotozoal drug that inhibits nucleic acid synthesis in micro-organisms. Since it was first introduced in 1959, metronidazole has been widely prescribed to treat pelvic inflammatory disease, endocarditis, and bacterial vaginitis. Metronidazole is functional in a partially reduced state under anaerobic conditions and should, therefore, be safe for humans. The major side effects of metronidazole include nausea, metallic taste, loss of appetite, and headache [1].

Optic neuropathy is a rare adverse event of metronidazole. We identified 10 cases of metronidazole-induced optic neuropathy in the literature (Table 1). Of these, 8 patients had spontaneous visual recovery and 2 patients had residual visual impairment. The time taken to develop optic neuropathy ranges from 1 week to 1 year. The youngest and oldest patients

| Table 1. Case series of metronidazole-induced optic neuropathy |
|------------------|-----------------|-----------------|-----------------|-----------------|
| Patients, n | Age, years | Dosage used, mg/day | Length of time to develop symptoms, days | Totally visual recovery, % |
|----------------|-------------|----------------------|--------------------------------------|--------------------------|
| McGrath et al. [2] | 1 | 67 | 1,200 | 180 | 100 |
| Bouraoui et al. [3] | 2 | 6–8 | na | 14 | 100 |
| Putnam et al. [4] | 7 | 26–53 | 750–1,000 | 7–365 | 71 |
| Peng et al. | 1 | 57 | 1,000 | 7 | 0 |

na, not available.
were aged 6 and 67 years, respectively. However, no dose-response relationship has been identified thus far (toxicity dosage = 750–1,200 mg/day) [2–4].

The underlying mechanism of neurotoxicity related to metronidazole remains unclear. Possible mechanisms include the accumulation of free radicals, dysregulation of neurotransmission, nutrition-deficiency-like neuropathy, and the inhibition of neuronal protein synthesis [1, 5]. After stopping the drug, neurotoxicities, such as encephalopathy, cerebellar syndrome, and peripheral neuropathy, had an excellent prognosis (days to weeks) [5].

Due to ethical concerns, we did not rechallenge our patient with metronidazole to confirm the direct causal effect. However, based on the Bradford Hill’s criteria for causation, it is highly likely that this patient’s optic neuropathy was caused by metronidazole. First, examining the timing, our patient developed visual and neurological symptoms after a 1-week course of metronidazole. Second, there is a specific association between this drug and the adverse effects. We have excluded other possible etiologies for optic neuropathy including infection, inflammation (seronegative NMO), and nutritional deprivation. In addition, despite that no biological gradient has been established for metronidazole optic neuropathy, the dosage that our patient received is within the range reported to trigger the visual complication (Table 1). Furthermore, from the view of pharmacokinetics, although the liver is the major organ for metronidazole metabolism, the final metabolites are excreted by the kidney. Our patient has ESRD, and it might be the accumulation of toxic metabolites of metronidazole that lead to the irreversible neurotoxicities. Last, similar findings of metronidazole-induced optic neuropathy have been discovered at different places and in different persons (the principle of analogy). However, previous patients suffering from neurotoxicities have satisfied outcomes after cessation of this agent. To the best of our knowledge, this is the first report of irreversible optic neuropathy related to metronidazole.

Statement of Ethics

This patient has given her written informed consent to publish. This study was approved by the IRB of Shin-Kong Wu Ho-Su Memorial Hospital. Information revealing the subject’s identity is to be avoided.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Pai-Huei Peng: conception and design; analysis and interpretation of data; drafting the manuscript; and final approval of the completed manuscript. Tzu-En Wu: acquisition of data; analysis and interpretation of data; and final approval of the completed manuscript. Ting-Yu Lin: drafting the manuscript and revising it for intellectual content; final approval of the completed manuscript.
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