

Amiodarone-Related Optic Neuropathy

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Background: To evaluate a case of atypical optic neuropathy that presented with blurred vision following the use of an antiarrhythmic agent.

Case: Record of the patient was reviewed to determine the etiology of his optic neuropathy.

Observations: Ophthalmological examination revealed unilateral optic disc edema with relatively well-preserved visual acuity. In routine tests, results of complete blood count, erythrocyte sedimentation rate, liver and kidney function tests, chest x-ray, Goldmann visual field examination, and brain computed tomography scan were normal. Orbital ultrasonography revealed optic disc edema with prominent optic nerve head and without orbital pathology.

Conclusions: Systemic history and drug intake should be investigated in every patient with optic disc edema. Discontinuation of the medication can prevent further optic nerve damage or involvement of the other eye. **Jpn J Ophthalmol 2000;44:565–568** © 2000 Japanese Ophthalmological Society

Key Words: Amiodarone optic neuropathy, ischemic optic neuropathy, toxic optic neuropathy.

Introduction

Amiodarone (Cordarone®) is administered in the treatment of symptomatic arrhythmia and angina pectoris. It is known to have ocular side effects, such as corneal microdeposits, subcapsular opacities, dysthyroid eye disease, enlargement of extraocular muscles, keratitis sicca, multiple chalazia, electrophysiologic abnormalities, and, more rarely, optic neuropathy. Corneal whorl-like opacities known as cornea verticillata are the most common (70–100%) side effect of the drug. This keratopathy does not affect vision and is, therefore, considered a benign, potentially reversible process.¹ More serious, systemic side effects, such as alterations in thyroid function (hypo- and hyperthyroidism), interstitial pneumonitis, drug interaction, dermatopathy, gastrointestinal problems, and peripheral neuropathy were reported, but fortunately most of them were reversible after treatment was discontinued.^{1,2} In this case report, optic neuropathy that was related to amiodarone is reported.

Case Report

A 51-year-old man was seen with the chief complaint of 10 days of blurred vision in his right eye. His visual acuity was 20/30 OD and 20/20 OS. No relative afferent pupillary defect (RAPD) was noted. Corneal whorl-like opacities were present in both eyes (Figure 1). Extraocular muscle functions were normal. Fundus examination of the right eye showed mild pale edema of the optic nerve head inferiorly with a small flame-shaped hemorrhage temporally. However, the retinal hemorrhage resolved in a few days and it was absent at the time of fundus photography (Figure 2A). Venous pulsation was absent. In the left eye, the optic nerve was normal with a C/D ratio of 0.2. Fundus fluorescein angiography showed fluorescein leakage from papillary vessels (Figure 2B). Due to hereditary color blindness, Ishihara color plates were not applicable. Goldmann perimeter showed a nonspecific central visual field constriction in the right and left eyes. VEP Recordings were normal in both eyes. The laboratory findings were as follows: erythrocyte sedimentation (ESR) rate was 17 mm/hour, complete blood count was normal, anti-streptolysin O was 200 Todd/unit, C-reactive protein, rheumatoid factor and hepatitis markers were

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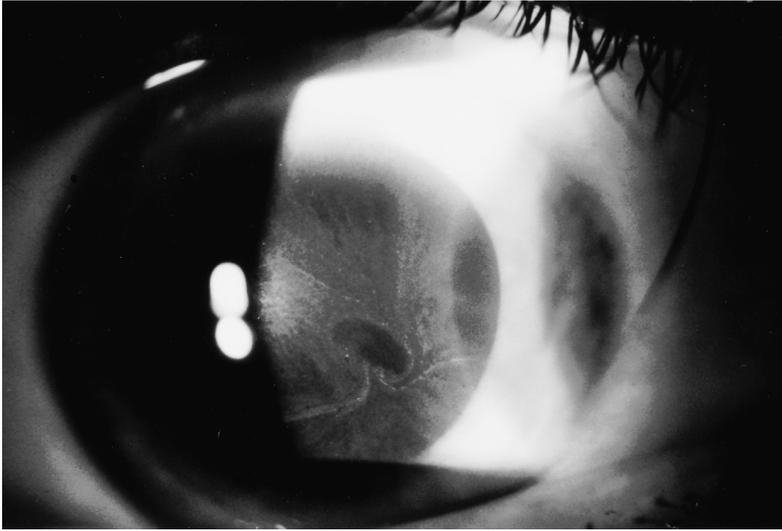


Figure 1. Corneal whorl-like opacities known as cornea verticillata in right eye of 51-year-old patient under treatment for heart problems.

negative. Orbital ultrasonography revealed a prominent optic nerve head consistent with optic disc edema, without any associated orbital pathology. Cranial computed tomography was reported as normal.

The patient had undergone balloon angioplasty 3 months previously and a pacemaker had been inserted because of atrial flutter. His blood pressure and glucose level were within normal range. Due to heart problems and arrhythmia he was given metoprolol (2×25 mg), digoxin (1×0.125 mg), acetylsalicylate 1×500 mg, and amiodarone 3×200 mg. He took amiodarone for 8 months in changing doses; for 3 months 3×200 mg and for 5 months 2×200 mg. After laboratory investigations and differential diagnosis of possible etiologies, the findings were thought to be related to amiodarone toxicity. Therefore, the patient was referred to his cardiologist for discontinuance of amiodarone. No additional treatment was given and he was called back for follow-up at 3 months.

At his final visit, visual acuity was 20/20 OU, with 1+ RAPD on the right eye. Corneal opacities disappeared 8 months after he stopped amiodarone. Optic discs looked pale inferiorly in the right eye and normal in the left. Goldmann visual field examination was the same as at his last visit.

Discussion

Amiodarone chlorhydrate, a triiodated benzofuran derivative, is a cationic amphiphilic drug possessing hydrophilic and hydrophobic groups that allow the drug to interact with polar lipids, and the resulting complexes accumulate in lysosomes as lamellated, membranous inclusion bodies.³ These in-

clusion bodies have been found in extraocular muscle fibers, corneal epithelial, stromal and endothelial cells, conjunctival epithelium, lens epithelium, scleral cells, iris, ciliary body, choroid, retina (particularly the retinal pigment epithelium and ganglion cells), large diameter axons of the optic nerve, and the endothelium of all ocular blood vessels.¹ Amiodarone has a high iodine content (37%), is extensively plasma protein-bound, and structurally similar to thyroxine; so treatment with amiodarone has been shown to cause production of anti-thyroid antibodies and anti-amiodarone antibodies. These substances can interact with the thyroid hormone metabolism, leading to hypo- or hyperthyroidism (thyrotoxicosis) and extraocular muscle enlargement. Most patients treated with amiodarone do not have ophthalmologic symptoms; different studies reported different prevalences, ranging between 0–11.4%.¹ The adverse effects of long-term therapy are related to the daily maintenance dose and to the cumulative dose (which is a function of the length of the therapy).

Amiodarone-induced optic neuropathy or papillopathy was previously described.^{2,4,5} Gittinger and Asdourian² reported on 2 of 150 patients treated with amiodarone for different periods. One of the patients had unilateral disc swelling with normal visual acuity and visual fields and the other patient had bilateral disc swelling with normal visual acuity. Sedwick⁶ described a patient taking amiodarone who had hypertension and diabetes and developed optic neuropathy. Visual loss was progressive despite discontinuation of the medication. Palimar and Cota⁵ suggested reversal or prevention of the side effects of amiodarone with administration of α -tocopherol.

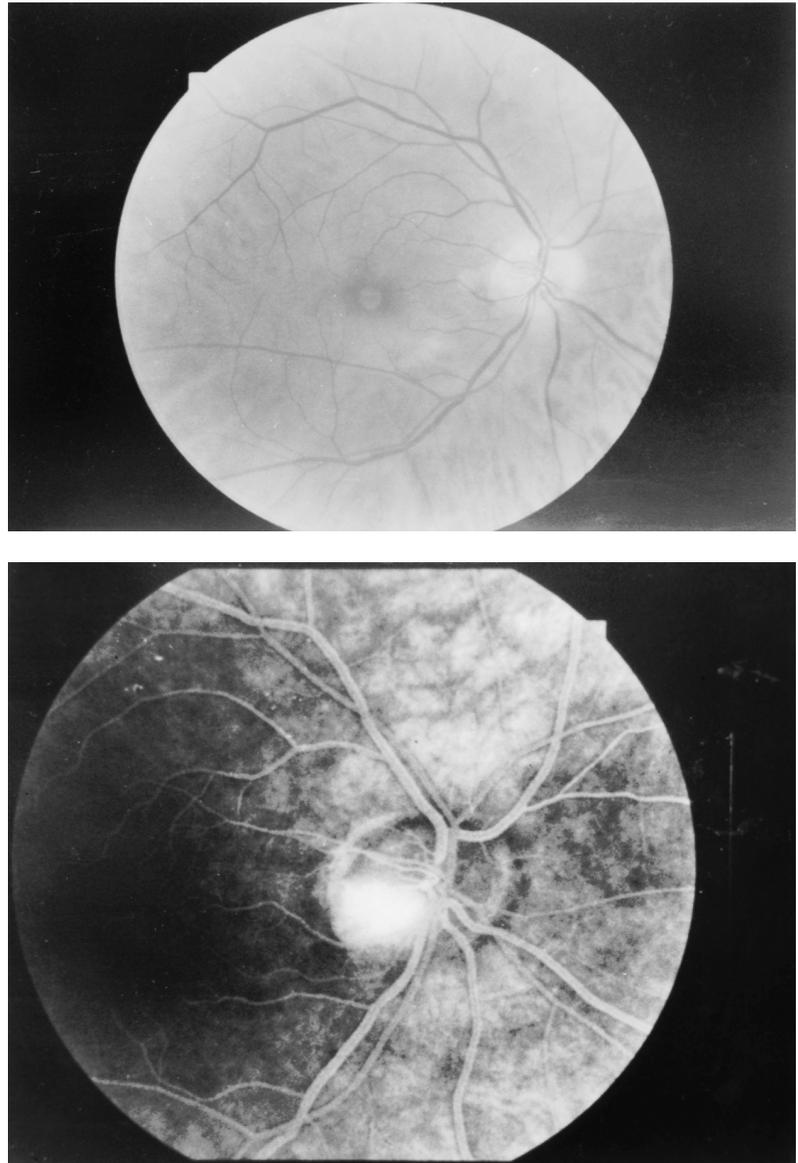


Figure 2. Fundus photography of right eye after resolution of (Top) flame-shaped retinal hemorrhage and (Bottom) fundus fluorescein angiography of right eye at mid-phase.

Nazarian and Jay⁷ reported a patient with mild, bilateral visual loss secondary to papillopathy and papilledema after 4 weeks of amiodarone therapy.

The initial diagnosis in our case was asymptomatic ischemic optic neuropathy with disc swelling. However, the visual acuity of the patient was well preserved without significant afferent pupillary defect or associated visual field changes in Goldmann perimetry. In addition, there were no associated local or systemic risk factors, such as hypotension, blood loss, anemia, surgery, or trauma history. Due to normal ESR, good visual acuity and the age of the patient, arteritic ischemic optic neuropathy was also ruled out, and temporal artery biopsy was not performed.

Even though there was no drug-related pattern (slow onset and bilaterality), reversal of the symptoms after discontinuation of the drug strongly suggested the role of amiodarone in the etiology. Both unilateral and bilateral optic neuropathy have been reported in amiodarone users.^{1,2,5} Recognition of symptoms in 1 eye may alert the physician so that discontinuation of the medication can prevent involvement of the second eye. Well-preserved visual function was accepted as a characteristic of amiodarone optic neuropathy but visual acuity can be variable.² The pathogenesis of amiodarone papillopathy may distinguish it from ischemic optic neuropathy. The lysosomal accumulation of amiodarone in

the cornea is well known and resembles the corneal deposits in Fabry disease and conditions in other patients receiving medications similar to amiodarone, including indomethacin, gentamicin sulfate, hydroquinone, chloroquine, perhexiline maleate, suramin sodium, tilorone, and monobenzenes. Amiodarone forms complexes with cellular phospholipids that cannot be metabolized by lysosomal phospholipases, and the accumulation of lysosomal inclusions may lead to periods of increased cellular and axonal permeability followed by compression and demyelination of nerves. Histopathological examinations of the optic nerve have revealed lamellar inclusions in the large axons and chronic neurotoxicity caused by drug-induced lipidosis.^{3,5} As the patients undergoing amiodarone therapy have associated cardiovascular diseases and a high risk for vaso-occlusive events, it is difficult to differentiate between drug toxicity and systemic vessel disease; however, preservation of vision and reversal of the symptoms after discontinuation of the drug strongly suggest amiodarone toxicity. Amiodarone-related optic neuropathy is milder than ischemic optic neuropathy. The therapeutic serum level of amiodarone is 0.5–2.0 $\mu\text{g/mL}$.¹ A serum level that can cause corneal deposits can also be a dose sufficient to cause retinopathy and optic neuropathy. The presence of corneal whorl-like opacities can be accepted as an indication of amiodarone toxicity. On the other hand, optic neuropathy is not seen in every patient with cornea verticillata, so

there may be an additional triggering factor or susceptibility for nerve involvement. Beside accumulation of the drug in the retinal cells or nerve fibers, sensitivity due to a drug elimination mechanism or hypersensitivity reaction can also play a role in the development of optic neuropathy.

Arrhythmia is a life-threatening medical problem, but treatment of this problem with amiodarone can cause a decrease in vision that becomes another disturbing complaint of the patient. The decision for discontinuation should be made after consulting with the patient's cardiologist. Optic neuropathy is usually self-limiting and reversible after discontinuation of the drug.

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