The Clinical Spectrum of Amiodarone-Associated Optic Neuropathy

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Purpose: To describe the clinical spectrum of amiodarone-associated optic neuropathy.

Methods: Observational cases series and review.

Results: Of 55 cases, the median interval for onset of optic neuropathy was four months after initiating amiodarone; 88% occurred within 12 months. Seven (13%) patients were asymptomatic. Twenty-two (40%) patients presented with sudden visual loss, while 26 (47%) had insidious loss of vision. Visual acuity ranged from 20/15 to light perception; 10 (18%) patients had legal blindness with visual acuity of 20/200 or worse. Visual field loss was present in 91% of cases. Color vision loss was present in eight (40%) of 20 cases. Optic disc edema was present in 85% of cases, while eight (15%) patients had retrobulbar optic neuropathy, without evidence of disc edema. Optic disc edema resolved over a median time of three months. Five patients had raised intracranial pressure on lumbar puncture.

Conclusion: We were able to classify amiodarone-associated optic neuropathy into five clinical categories with respect to temporal characteristics and optic nerve appearance: insidious-onset (43%), acute-onset (28%), retrobulbar (13%), increased intracranial pressure (8%), and delayed-progressive onset (8%). Most cases of optic neuropathy commenced within 12 months of initiating amiodarone, with the median onset being four months. Over 10% of patients will have no visual symptoms at the onset. Ophthalmologic examinations within the first 12 months—and particularly within four months of initiating amiodarone—should improve early detection of amiodarone-associated optic neuropathy.

Key words: amiodarone ■ optic neuropathy ■ vision loss ■ retrobulbar ■ visual field loss

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INTRODUCTION

In 1984, Ghosh and McCulloch[1] presented the ocular histopathological findings from two patients who had died after protracted treatment with amiodarone. One patient had received 600 mg daily for 18 months, and the other patient received from 600 mg to 1,200 mg daily for 30 months. These two patients had membrane-bound intracytoplasmic lamellar and granular bodies throughout the eyes, including the retinal ganglion cells. With prescience, Ghosh and McCulloch[1] asked, "Would a higher dose of amiodarone and a longer duration of therapy cause more ganglion cells to be affected and perhaps produce irreversible visual damage?" In part, this conjecture resulted from these investigators having mentioned in 1982 the first report of a patient developing "ischemic optic neuropathy" following amiodarone use.[2] No further information was provided about this case apart from the designated diagnosis. Subsequently, other investigators have reported optic neuropathy as a complication of amiodarone use.[3-27] Legal settlements attributed to blindness in association with amiodarone-associated optic neuropathy have been costly.[28,29]

Macaluso et al.[30] sought to characterize amiodarone-associated optic neuropathy to differentiate this entity from nonarteritic anterior ischemic optic neuropathy (NAION), the most common optic nerve disorder producing sudden vision loss in the elderly.[31] NAION occurs at an incidence rate of 2.3 to 10.2 per 100,000 individuals over the age of 50 years, resulting in at least 6,000 new cases of NAION each year in the United States.[31-33] The reported incidence of amiodarone-associated optic neuropathy is 1.79% among individuals using amiodarone.[4] Macaluso et al.[30] pooled data from 73 cases of amiodarone-associated optic neuropathy; 57 cases were culled from the National Registry of Drug-Induced Ocular Side Effects, the U.S. Federal Drug Administration, and the World Health Organization, and the remaining 16 cases were from three published case series. Information from registries can be too scant to assess the spectrum of clinical presentation of a disease. Indeed, Macaluso et al.[30] identified that a shortcoming of their study was the incom-

plete data on many of the patients. In contrast to registry data, published case reports may yield clinical information to characterize amiodarone-associated optic neuropathy. Since the initial report of amiodarone-associated optic neuropathy, over 40 cases have been published.[3-27] We present an analysis of these cases and 11 cases we have personally evaluated to increase our understanding of the clinical spectrum of amiodarone-associated optic neuropathy.

Subject and Methods

We defined amiodarone-associated optic neuropathy as optic neuropathy occurring while using amiodarone. Patients were excluded if there was a prior history of visual loss from optic nerve disorder or if ocular or systemic disorders (e.g., acute hypotension, diabetic retinopathy, orbital tumors, etc.) were present that could cause the optic neuropathy.

A Medline search was undertaken using the following search words: anterior ischemic optic neuropathy, optic neuropathy, optic neuritis, optic nerve, papilledema, pseudotumor, and optic disc edema in combination with amiodarone (Cordarone and Pacerone, Wyeth-Ayerst Laboratories of American Home Products Corporation, Madison, NJ, and Upsher-Smith Laboratories, Inc., Minneapolis, MN,

Table 1. Summary of the Clinical Presentations and Outcomes of the 55 Cases of Amiodarone-Associated

Total Cases	*Reference*	*Case # in series*	*Unilateral/ Bilateral*	*Age/ Sex*	*Duration Amiodarone use (mos)*	*Dose (mg/da)*	*Corneal Keratopathy*	*Presenting Symptom*	*Presenting Visual Acuity, Color, Pupil*	*Presenting Visual Field*
1	Gittinger (1987)	1	U	45 M	6	?1200	Y	routine exam	20/20 OU normal color	normal OU
2	Gittinger (1987)	2	B	61 M	2	400	Y	hazy vision OD	20/25 OU normal color pupil: APD OD	Bjerrum OD
3	Feiner (1987)	1	U	71 M	4	400	Y	sudden vision loss OS	20/20 OD 20/400 OS	constriction OS
4	Feiner (1987)	2	U	64 F	2	400	Y	sudden visual blur OD	20/30 OD 20/25 OS	depression OD
5	Feiner (1987)	3	U	65 F	4	200-600	N	routine exam	20/20 OU	depression OD
6	Feiner (1987)	4	B	54 M	3	200-600	N	sudden shadow OS	20/20 OU	arcuate OU
7	Feiner (1987)	5	B	71 M	1	200-600	N	sudden vision loss OD	20/200 OD 20/20 OS	centrocecal OD
8	Feiner (1987)	6	U	73 M	12	200-600	Y	sudden vision loss OS	Count Finger OD (previous neuroretinitis and macular scar) 20/25 OS	old scotoma OD depression OS
9	Feiner (1987)	7	U	62 M	5	200	N	routine exam	20/20 OD 20/25 OS	inferior nasal OS
10	Feiner (1987)	8	U	71 M	4	200-600	N	routine exam	20/25 OD 20/50 OS	depression OS
11	Feiner (1987)	9	B	64 M	12	400	Y	vision loss OU	20/30 OD 20/25 OS	arcuate OU
12	Feiner (1987)	10	U	52 M	3	200-600	N	visual blur OS	20/15 OD 20/20 OS normal color pupil: APD OS	arcuate OS
13	Feiner (1987)	11	B	63 M	6	200-600	Y	vision loss OS	20/30 OD 20/60 OS pupil: APD OS	inferior altitudinal OD, central OS

ODE: Optic disc edema.

respectively). A total of 47 cases of amiodarone-associated optic neuropathy was identified in the world literature.[3-27,34,35] Three cases were excluded due to the following: 1) the first case by Sreih et al.[14] appeared to have been sequential idiopathic NAION, with the initial NAION event occurring six years prior to the patient's use of amiodarone; 2) one case had visual loss from a craniopharyngioma in addition to amiodarone use;[34] and 3) one case had optic disc appearance suggesting buried optic disc drusen in the setting of infantile cardiac arrests and stroke, with no history of prior visual testing to corroborate if changes in visual function were new or long-standing.[35]

Optic Neuropathy.

Hypertension	*Diabetes*	*Optic Disk*	*Outcome*
N	N	ODE OS	Amiodarone continued ODE OS resolved -1 mos Vision - no change
Y	N	ODE OD, few days later ODE OS	Amiodarone decreased 200 mg ODE OS resolved - 7 mos ODE OD resolved - 8 mos VA 20/20 OU VF-constriction
N	Y	ODE OS	Amiodarone continued Optic atrophy OS Vision - no change peripheral neuropathy
N	N	ODE OD	Amiodarone continued ODE OD resolved - 3 mos Vision - no change
N	N	ODE OD	Amiodarone continued Vision - no change
N	N	ODE OU	vision worse over next 7 mos, then Amiodarone stopped bilateral optic atrophy - 7 mos 20/20 OD; 20/100 OS VF-constriction OU
N	Y	ODE OD, in retrospect ODE OS	Amiodarone stopped, but 1 mos later 20/20 and centrocecal OS, ODE OD resolved - 1 mos, Optic atrophy, ODE OS
Y	N	ODE OS	Amiodarone continued Vision - no change; Died 14 mos later
N	N	ODE OS	Amiodarone continued Optic atrophy OS Vision - no change
Y	N	ODE OS	Amiodarone stopped Vision - no change
N	N	ODE OU	?
?	?	ODE OS	Amiodarone continued ODE OS resolved - 2 mos, optic atrophy Vision - no change
?	?	ODE OS	Amiodarone continued Vision: worse OD; count finger OS

We also reviewed the medical records of patients with optic neuropathy evaluated from 1990 to 2002 at our respective Neuro-Ophthalmology Services. Approval was obtained from the Institutional Review Board to perform the search. Of 812 patients with the diagnosis of optic neuropathy, 21 (3%) patients had visual loss in association with amiodarone use. Of these 21 cases, 10 were excluded because of comorbid diseases that could have caused the optic neuropathy, such as proliferative diabetic retinopathy, end-stage renal disease, acute hypotension, cardiac arrest, and traumatic subdural hemorrhage. The remaining 11 cases were included in our analysis of amiodarone-associated optic neuropathy.

Illustrative Cases

Case 1. A 78-year-old man with hypertension of 10 years' duration developed atrial fibrillation in 1995. Amiodarone was initiated in February 1997. Three months later, in May 1997, he experienced sudden loss of vision in the right eye. Examination at that time documented visual acuity of 20/60 OD (right eye) and 20/400 OS (left eye), despite a normal left optic nerve appearance. The right eye showed moderate optic disc edema with optic disc hemorrhage. Westergren erythrocyte sedimentation rate was normal. One month later, in June 1997, he noted loss of vision in the left eye. Examination documented light perception vision OD and finger counting vision OS. There was moderate optic disc edema in both eyes. A magnetic resonance imaging (MRI) scan showed mild cerebral atrophy. Temporal artery biopsy was normal. Amiodarone was discontinued in June 1997. In the intervening years, he has not observed any change in his vision. Examination in January 2002 documented light perception vision OD and 3/200 vision OS, a marked (2.1 log units) right afferent pupillary defect, and marked optic atrophy bilaterally.

Case 2. A 71-year-old man was evaluated following multiple episodes of unilateral superior visual field amaurosis lasting three-to-four minutes each. He had a history of atrial fibrillation and had undergone successful aortic valve replacement. Amiodarone 400 mg daily had been initiated four months previously. He also was taking low-dose aspirin and warfarin. Visual acuity was 20/25 in each eye, and automated perimetry was normal. Pupillary responses were normal. Corneal verticillata was present bilaterally. The optic nerves were normal. A brain MRI scan and magnetic resonance angiogram of the carotid arteries were normal. Westergren erythrocyte sedimentation rate was normal. The amiodarone was stopped that day, and the amaurotic episodes abated within two days. When the patient was evaluated 30 days later, he was asymptomatic, but the amiodarone level remained

at near-therapeutic levels at 0.9 mcg/ ml (reference range 1.0–2.5 mcg/ml). Visual acuity was 20/25 OD. A right inferior arcuate scotoma was identified on automated perimetry. A right afferent pupillary defect of 0.3 log units was present. There was nasal optic disc edema with splinter hemorrhages on the disc margin. The edema subsided over a one-month period, leaving temporal pallor and an acuity of 20/30 OD.

Case 3. A 57-year-old man was evaluated for a two-week history of blurred vision. He had been treated for six weeks with 400 mg daily of amiodarone for atrial fibrillation. Visual acuity was 20/25 OD and 20/300 OS. Bilateral optic disc edema was present, and automated perimetry revealed inferior arcuate scotomas OU (both eyes). His corneas were normal. Erythrocyte sedimentation rate and brain MRI scan were normal. A spinal tap revealed an

Table 1 continued

14	Feiner (1987)	12	B	58 M	72	200	N	vision loss OU	20/70 OD 20/60 OS	increased blind spot OD
15	Feiner (1987)	13	U	67 M	10	400	N	Ataxia; routine exam	20/50 OD 20/30 OS	visual field normal OU, abnormal VEP OS
16	Dewachter (1988)	1	B	52 M	3	400	Y	gradual visual loss OS	12/10 OD {20/16} 10/10 OS {20/20} normal color, VEP	constriction OS
17	Nazarian (1988)	1	B	56 M	1.5	800	Y	rapid visual loss OS	20/25 OD count finger OS pupil: APD OS	central OS
18	Garrett (1988)	1	B	51 M	3	800	Y	gradual vision loss OU; tremor, ataxia	20/30 OU normal color normal-EOG, ERG,VEP	constriction OU
19	Ferreiro (1990)	1	B	50 M	18	800 x 3 mos, 600 x 10 mos,300 x 5 mos	?	gradual vision loss OS	9/10 OD {20/25} 5/10 OS {20/40} abnormal VEP OU	inferior altitudinal OS
20	Ferreiro (1990)	2	B	61 M	24	400 x 20 mos,200 x 4 mos	?	gradual vision loss OS	8/10 OD {20/25} 6/10 OS {20/30} abnormal VEP OU	constriction OS
21	Sedwick (1992)	1	B	62 F	12	?	Y	sudden vision loss OS	20/15 OD count finger OS pupil: APD OS	central OS
22	Krieg (1992)	1	B	62 M	3	200	Y	vision loss OS	1.0 OD {20/20} 0.7 OS {20/30} pupil: APD OS	arcuate OS
23	Belec (1992)	1	B	55 M	17	200	Y	vision loss OS	7/10 OU {20/30} abnormal VEP OU	inferior defect OS
24	Seemongal-Dass (1998)	1	B	56 M	1.5-symptom began 3 - exam	200 x 1 mos,100 x 2 mos	N	vision loss OS	6/5 OD {20/15} 6/6 OS {20/20}	depression OU
25	Palimar (1998)	1	B	58 M	2	400	Y	acute vision loss OS	6/5 OU {20/15} pupil: APD OS	inferior altitudinal OS
26	Sreih (1999)	2	B	74 M	4	?	N	Progressive vision loss OD	20/400 OD 20/50 OS pupil: APD OD	?
27	Sreih (1999)	3	B	65 M	12	?	Y	Visual blur	20/25 OU	paracentral & arcuate OD nasal island OS

opening pressure greater than 300 mmH_2O, with normal protein, glucose, and cytology. We recommended that he stop the amiodarone; however, this was not done. Optic nerve sheath fenestration was performed on the left side. His amiodarone was discontinued one month later. His disc edema subsided over several months, leaving him with bilateral optic atrophy, although his visual acuity improved to 20/20 OD and 20/20- OS.

N	N	ODE OU	Amiodarone stopped "acuity was normal except slight impairment" OD
N	N	normal	Amiodarone stopped VA and VEP slowly improved 8 mos
N	N	ODE OU	Amiodarone stopped ODE resolved - 2 mos VF defect -improved Lumbar puncture - normal
Y	N	ODE OU	Amiodarone stopped ODE resolved - 4 mos Optic atrophy - OU Vision worse: 20/50 & centrocecal OD, 20/200 & island remaining OS Lumbar puncture - 160-240 mmH20
N	N	ODE OU	Amiodarone stopped ODE resolved - 7 mos Optic atrophy OU VA 20/20 OU; VF- worse constriction Lumbar puncture - 190-238 mmH20
Y	N	ODE OU	Amiodarone stopped ODE resolved - 8 mos Optic atrophy - OS VA: 9/10 OD {20/25}, 7/10 OS {20/30} Lumbar puncture - normal
N	N	ODE OU	Amiodarone continued Died w/i 1 mos
Y	Y	ODE OS, shortly after ODE OD	Amiodarone stopped ODE OS resolved - 2 mos, ODE OD resolved - 3 mos Optic atrophy - OU VA 20/70 OD; 20/400 OS
Y	N	ODE OD Optic atrophy OS	Amiodarone stopped Vision worsened ODE resolved and optic atrophy OU
N	N	ODE OU	Amiodarone stopped ODE resolved - 7 mos VA 8/10 OU {20/25} VF -unchanged Lumbar puncture - normal
N	N	ODE OD Optic atrophy OS	Amiodarone stopped ODE resolved - 1 mos Optic atrophy - OU VA 6/24 OD {20/80} VA 6/5 OS {20/15} TA Bx - negative Lumbar puncture - normal
Y	N	ODE OS	Amiodarone stopped, but 6 wks later ODE OD, VF defect OD Vision unchanged
?	?	ODE OU	Amiodarone stopped Vision - unchanged
?	?	ODE OU	Amiodarone stopped Vision - unchanged Lumbar puncture - normal

RESULTS

Tables 1 and 2 summarize the 55 cases of amiodarone-associated optic neuropathy. These cases represent 44 published cases and our 11 cases. There was a predominance of men being represented among the cases of amiodarone-associated optic neuropathy, with there being 48 (87%) men and seven (13%) women. The mean and median ages for the group were identical at 62 years (range: 32–84 years). There were 20 (39%) patients with hypertension and six (12%) with diabetes mellitus, of the 51 cases for which this information was provided.

Only one patient had received intravenous amiodarone; optic neuropathy occurred within 72 hours of receiving a total of 6 g.[15] All other cases of optic neuropathy occurred during oral ingestion. Amiodarone-associated optic neuropathy developed within three days to 72 months of initiating amiodarone, with the median and mean time intervals being four months and eight months, respectively. Amiodarone-associated optic neuropathy occurred within 12 months of initiating amiodarone for 46 (88%) of 53 cases. The dose of amiodarone ranged from 100 mg to 1,200 mg daily (median: 400 mg daily). Over 80% of patients were treated with amiodarone of 400 mg or less daily. Only five patients received 800 mg or more daily.

Funduscopic examination revealed optic disc edema in 47 (85%) of 55 cases. Twenty-eight (51%) of the 55 patients had bilateral and simultaneous optic disc edema, while 19 (35%) of the 55 patients presented with unilateral optic disc edema. Seven (37%) of the 19 patients demonstrated optic disc edema in the fellow eye on follow-up examination.

In 24 patients, the duration of optic disc edema was reported. The median duration of optic disc edema was three months (range: one-to-eight months). Eight (15%) of the 55 cases had no evidence of optic disc edema; vision loss in this group was due to retrobulbar optic neuropathy. Following the bout of optic neuropathy, either with or without optic disc edema, optic nerve pallor (atrophy) was subsequently reported in 17 (32%) of 53 cases.[36]

Seven (13%) of the 55 cases were asymptomatic. Of these seven cases, six had optic disc edema, and one had retrobulbar optic neuropathy without optic disc edema. One asymptomatic patient had bilateral optic disc edema and increased intracranial pressure (235 mmH_2O). Another patient (Case 39) had unilateral optic disc edema with fellow eye disc edema occurring three weeks *after* discontinuing amiodarone.

Clinical symptoms on presentation were nearly equally divided among the 48 individuals with visual loss. Twenty-two (40%) of 55 cases presented with sudden visual loss, and 26 (47%) of 55 cases had insidious loss of vision. Of note is that four patients with sudden visual loss from amiodarone-

associated optic neuropathy had optic nerve cup-disc ratio of 0.2–0.5, and one patient had absent optic nerve cup. Although 32 (58%) of 55 cases patients reported visual loss affecting only one eye, 18 (56%) patients had evidence of bilateral and simultaneous optic disc edema at the time of presentation. Two of these 18 patients had documented pseudotumor cerebri. Five (9%) of 55 cases patients had initial unilateral optic disc edema, but subsequently developed bilateral optic disc swelling. In four of these five cases (Cases 7, 25, 37, 46), optic disc edema developed a few days to six weeks *after* discontinuing amiodarone (delayed-progressive optic neuropathy). For Case 7, minimal capillary disturbance and optic disc edema were noted only in retrospective examination of fundus photographs taken at the time of initial examination.[4]

Sixteen (29%) of the 55 cases presented with bilateral visual symptoms. All 16 cases demonstrated bilateral optic nerve involvement; 10 (18%) of 55 cases of whom had bilateral optic disc edema. The remaining six (11%) of 55 cases of the 16 cases had

Table 1 continued

28	Bartolucci (1999)	1	B	66 M	3 days (*IV*)	6 gms in 72 hrs IV	N	Acute visual blur OU	20/200 OD count finger OS	central and constriction OU
29	Gobbele (1999)	1	B	66 F	5	600	Y	gradual vision loss OU	0.5 OD {20/40} 1/50 OS {4/200}	constriction OU
30	Speicher (2000)	1	B	48 M	?	400	Y	hazy vision OU	20/20 OU normal color normal pupil	arcuate OU
31	Eryilmaz (2000)	1	U	51 M	8	600 x 3 mos,400 x 5 mos	Y	acute vision loss OD	20/30 OD 20/20 OS hereditary color blindness	constriction OU normal-VEP
32	Leifert (2000)	1	B	70 M	4	200	Y	gradual vision loss OD	0.4 OD {20/50} 0.8 OS {20/25} color 6/15 OD, 13/15 OS	nasal OD arcuate OS
33	Leifert (2000)	2	B	55 M	7	200	Y	gradual vision loss OS	1.0 OD {20/20} 0.9 OS {20/25} pupil: APD OS	inferior arcuate OS
34	Leifert (2000)	3	B	62 M	3	200	Y	acute vision loss OU	0.2 OU {20/100}	inferior altitudinal OU
35	Kristin (2001)	1	B	69 M	?	?	Y	acute vision loss OS	0.8 OD {20/25} 0.63 OS {20/30} abnormal color	nasal OU
36	Polak (2001)	1	B	69 M	2	200	Y	gradual vision loss OU	1/300 OD light perception OS	central OU
37	Uebermuth (2002)	1	B	79 M	18	400	Y	gradual vision loss OD; vision loss OS 6 weeks later	1/50 OD {4/200} 0.2 OS {20/100} normal color OU	constriction OU
38	Castells (2002)	1	B	76 M	1	200	Y	gradual vision and color loss OU	20/50 OD 20/60 OS color 4/10 OU	normal OU
39	Nagra (2003)	1	B	72 M	3	200	N	ataxia, routine exam	20/30 OD 20/60 OS color 10/10 OD, 0/10 OS; APD OD	inferior arcuate OS, depression OD
40	Nagra (2003)	2	B	70 M	7	200	Y	vision loss OS	20/60 OU normal color normal pupil	arcuate / nasal OU
41	Nagra (2003)	3	B	59 M	3	800 x 2 mos,200 x 1 mos	Y	dark vision OS	20/25 OD 20/60 OS color 11/11 OD, 5/11 OS	inferior altitudinal OU
42	Fikkers (1986)	1	B	58 M	6	400	Y	acute vision blur OD	1.0 OU {20/20}	inferior defect OD

normal optic discs, with the cause of visual loss being bilateral retrobulbar optic neuropathy.

Visual acuity at the time of presentation ranged from 20/15 to light perception. The median visual acuity was 20/30, and 32 (58%) patients had 20/40 or better visual acuity. Ten (18%) patients (Cases 3, 7, 17, 21, 26, 29, 36, 37, 47, 55) had legal blindness, with visual acuity of 20/200 or worse on initial presentation. Of the 50 cases in whom visual acuity on follow-up was reported, 20 (40%) cases had improved, five (10%) cases had worsening of vision, and 25 (50%) had no change in vision. Two patients who presented with count fingers vision improved to 20/200 and 20/400. However, three patients with initial 20/60 visual acuity had worsened acuity to count fingers and light perception.

N	N	normal OU	Amiodarone stopped Vision returned - Normal
N	N	ODE OU	Amiodarone stopped Vision improved 0.5 OD {20/40} 0.2 OS {20/200} Lumbar puncture - normal
N	N	normal OU C/D 0.4 OU	Amiodarone stopped Vision improved in 3 mos
N	N	ODE OD C/D-0.2L	Amiodarone stopped 20/20 OD, +APD OD, ODE resolved, Optic atrophy
Y	Y	ODE OU	Amiodarone stopped ODE resolved - 5 mos Vision improvement 0.7 OD {20/30}; 1.0 OS {20/20} color - 13/15 OD; 14/15 OS
N	N	ODE OU	Amiodarone stopped Vision improvement VA 1.2 OU {20/15}
Y	Y	ODE OU	Amiodarone stopped Vision improvement VA 0.6 OU {20/30} ODE resolved, Optic atrophy
Y	N	ODE OU	Amiodarone stopped ODE resolved - 4 mos
Y	N	ODE OU	Amiodarone stopped Vision not improved
N	N	ODE OD, later ODE OS	Amiodarone stopped Vision loss OS 6 weeks after discontinuing amiodarone
Y	N	normal OU	Amiodarone stopped Vision improved 20/30 OU, color - 10/10 OU
N	N	ODE OD, 3 weeks later ODE OS	Amiodarone stopped Vision improved 20/30 OD, 20/40 OS; Color 7/10 OD, 6/10 OS; VF improved; ODE resolved 7.5 mos
N	N	ODE OU	Amiodarone stopped Vision improved 20/30 OD, 20/40 OS; ODE resolved 8 mos
Y	N	ODE OU	Amiodarone stopped Vision improved 20/25 OD, 20/40 OS; Color 11/11 OD, 9/11 OS; VF improved OD, but no change OS; ODE resolved 6 mos
Y	N	ODE OU	Continued Amiodarone x 12 mos after; VA -worse (1.25 OD {20/15}, 0.8 OS {20/25}, then Amiodarone stopped Optic atrophy OU; VA - improved to normal; VF defect -OD; Lumbar puncture - 300 mmH20

Visual field at the time of presentation was normal in only five (9%) of 53 cases. Arcuate or altitudinal scotomas were found in 24 (45%) cases, constriction or depression in 15 (28%) cases, central or centrocecal scotomas in eight (15%) cases, and increased blind spot in one (2%) case. In contrast to visual acuity, the visual field loss generally was permanent.

Color vision was reported in 20 cases, of which eight (40%) developed acquired color vision loss.

Amiodarone keratopathy, as manifested by corneal verticillata on slit-lamp biomicroscopy, was observed in 35 (66%) of 53 patients. Amiodarone-associated optic neuropathy occurred within six months of initiating amiodarone therapy for 19 (54%) of the 35 patients who had amiodarone keratopathy. Likewise, amiodarone-associated optic neuropathy occurred within six months in 13(72%) of 18 patients without amiodarone keratopathy.

Lumbar puncture was performed for 12 patients. Cerebrospinal fluid analysis was generally normal, but in some cases there was slightly increased cerebrospinal fluid protein with normal cell count. In five (9%) of 55 cases patients, the intracranial pressure was greater than 200 mmH_2O (Cases 17, 18, 42, 44, and 47), ranging from 235 to 300 mmH_2O. Two (4%) of 55 cases patients (Cases 42 and 47) satisfied the modified Dandy criteria for diagnosis of pseudotumor cerebri with intracranial pressure greater than 250 mmH_2O.[37]

DISCUSSION

The classic presentation of amiodarone-associated optic neuropathy has been reported as insidious in onset, simultaneous and bilateral, and with visual acuity ranging from 20/20 to 20/200.[30] Our case review shows that the clinical profile of amiodarone-associated optic neuropathy is not as stereotyped as previously described. Vision loss is not always insidious. Rather, a sudden onset is almost as common as the insidious presentation. Additionally, although most cases of amiodarone-associated optic neuropathy present with bilateral optic neuropathy, 35% of patients initially will have unilateral optic disc edema. In time, many of these unilateral cases became bilateral. On the basis of these 55 cases, we were able to classify amiodarone-associated optic neuropathy into five clinical categories (Table 3) with respect to temporal characteristics (insidious, acute onset, delayed progressive) and optic nerve appearance (presence or absence of optic disc edema).

The most common form of amiodarone-associated optic neuropathy is an insidious onset, which occurred

in approximately 40% of cases. These patients generally have bilateral and simultaneous optic disc edema, despite many reporting visual loss in only one eye. The second most common form, occurring in almost 30% of cases, is an NAION-like picture with acute unilateral or bilateral visual loss.[38-41] The third form of amiodarone-associated optic neuropathy, occurring in almost 15% of cases, is that of retrobulbar optic neuropathy. The visual loss in the retrobulbar cases occurs insidiously or acutely, and it may occur in only one eye or both eyes simultaneously. Patients with retrobulbar optic neuropathy from amiodarone are the most difficult to diagnose and will require neuroradiologic imaging to rule out a mass lesion, as well as appropriate blood studies to rule out other etiologies of visual loss in the setting of normal optic nerves. The fourth category, accounting for almost 10% of cases, is increased intracranial pressure greater than 200 mmH_2O. Of the five patients with raised intracranial pressure, one was asymptomatic, two had acute visual loss, and two had insidious visual loss. All five patients had bilateral and simultaneous optic disc edema, but none had other

Table 1 continued

43	Van Zandijcke (1986)	1	B	52 M	3	400	Y	gradual vision loss OS	normal acuity normal color	inferior defect OS
44	Grogan (1987)	1	B	51 M	5	800	Y	tremor; routine exam	VA - normal	normal OU
45	Johnson	1	B	78 M	3	400	Y	acute visual loss OD, later visual loss OS	20/60 OD 20/400 OS	central OD
46	Johnson	2	U	71 M	4	400	Y	acute visual loss OD (amaurosis fugax)	20/25 OU	inferior arcuate OD
47	Johnson	3	B	57 M	1.5	400	N	insidious blur vision OS x 2 wks	20/25 OD 20/300 OS	inferior arcuate OU
48	Johnson	4	B	60 M	24	600	Y	visual blur OU	20/60 OU color 4/15 OD, 7/15 OS	constriction OU
49	Johnson	5	B	32 F	22	100	N	intermittent visual loss OU	20/20 OU normal color normal pupil	arcuate OD mild depression OS
50	Johnson	6	B	63 M	6	400	Y	intermittent visual loss OU	20/25 OD 20/40 OS color 16/17 OD, 15/17 OS pupil: APD OS	normal OU
51	Johnson	7	U	81 F	12	400	N	visual loss OD, headache	20/70 OD 20/40 OS color 13/15OU	depression OU
52	Johnson	8	U	44 M	2	400	N	acute visual loss OD	20/25 OD 20/15 OS color 16/17 OD, 17/17 OS	central OD
53	Johnson	9	U	69 M	2	400	Y	visual blur OU	20/20 OU pupil: APD OD; color 17/17 OU	arcuate OD
54	Johnson	10	B	81 F	1	600	N	acute visual loss OU	20/30 OD 20/25 OS color 0/17 OD, 11/17 OS	depression OU
55	Johnson	11	B	84 M	9	400	N (2 months later, Y)	gradual vision loss OU, dry macular degeneration OS	20/80 OD 20/400 OS	depression OU

signs or symptoms of pseudotumor cerebri, such as headache and abducens (cranial nerve VI) palsy. The intracranial pressure in two patients with raised intracranial pressure was greater than 250 mmH_2O, satisfying the modified Dandy criteria for diagnosis of pseudotumor cerebri.[37] The fifth category of amiodarone-associated optic neuropathy is delayed-progressive onset, occurring in approximately 10% of cases. These patients may report visual loss before the appearance of optic disc edema and may also acquire optic disc edema several days to weeks after amiodarone is withdrawn, because of the long half-life of amiodarone (from 35 to 110 days).[42-45] The blood level of amiodarone may even rise during one- to two weeks after cessation of drug therapy. Indeed, one of our patients developed optic disc edema four weeks after stopping the drug. His amiodarone level was near-therapeutic at 0.9 mcg/ml, 30 days after stopping the drug.

Y	N	ODE OU	Amiodarone stopped ODE resolved - 2 mos Vision - improve but still VF defect Lumbar puncture - normal
N	N	ODE OU	Amiodarone stopped ODE resolved Lumbar puncture - 235 mmH20
N	N	ODE OD; 1mos later ODE OS	cataract OS Amiodarone stopped, Vision worse: light perception OD; 20400 OS:
Y	N	normal OU; 6 weeks later ODE OD	Amiodarone stopped; amiodarone level 0.9 mcg (therapeutic 1-2.5) 30 days later Delayed Onset, 20/20+ OU, ODE resolved - 1.5 mos, Optic atrophy
Y	N	ODE OU	Amiodarone continued, optic nerve sheath fenestration OS; then Amiodarone stopped; 20/20 OD; 20/25 OS ODE resolved - 3 mos, Optic atrophy OU Lumbar puncture - 300 mmH_20
N	N	normal OU C/D 0.4 OD, 0.3 OS	Amiodarone stopped Vision worse 20/400 & constriction OD; count finger & absolute scotoma OS; pulmonary fibrosis
N	N	normal OU C/D 0.0OU	Amiodarone stopped Vision no change 2 thyroid tumors
Y	Y	ODE OS C/D 0.0OU	Amiodarone continued Vision no change, ODE OS resolved - 3 mos
N	N	ODE OD C/D 0.1OD 0.2 OS	Amiodarone stopped VA improve 20/60 OD; 20/30 OS; VF - normal ODE resolved
N	N	normal OU C/D 0.3OU	Amiodarone stopped (3 days prior to onset of visual loss); Vision no change
Y	N	normal but peripapillary capillary prominence OD; C/D 0.0OU	Amiodarone reduced 200 mg; Vision - no change
N	N	Optic atrophy OU C/D 0.5OU	Amiodarone reduced 200 mg
Y	N	Optic atrophy OU	Amiodarone continued; vision unchanged; optic atrophy OU

Contrary to the report by Macaluso et al.[30] indicating maximum visual acuity loss of 20/200 for amiodarone-associated optic neuropathy, our review suggests that nearly 20% of patients with amiodarone-associated optic neuropathy have legal blindness, with 20/200 or worse visual acuity on initial presentation. While 40% of patients experience some improvement in visual acuity, most patients will have no change in visual acuity after amiodarone withdrawal. Additionally, 10% will have a further decline in visual acuity even after discontinuing the drug. Following a bout of optic neuropathy, either with or without optic disc edema, optic atrophy may ensue. Optic atrophy, as manifested clinically by optic nerve pallor, is generally a harbinger of irreversible visual field loss.[36] Consequently, in contrast to visual acuity loss, visual field loss is frequently permanent despite cessation of amiodarone.

Dyschromatopsia has been reported with amiodarone use.[46-49] In an earlier study, Duff et al.[50] reported color vision defect on Farnsworth-Munsell 100 Hue test in a group of patients taking amiodarone for 16 months or more. These investigators considered the color vision defect to be related to the extent of amiodarone keratopathy (corneal verticillata). More recently, however, Ikäheimo et al.[51] identified blue color vision defect as an early manifestation of amiodarone-associated optic neuropathy, irrespective of the degree of keratopathy. In the present case series, acquired color vision loss was diagnosed in 40% of 20 cases in whom color vision status was reported.

Almost 30% of cases with the acute-onset form of amiodarone-associated optic neuropathy had a clinical picture similar to NAION, with sudden and painless loss of vision accompanied by optic disc edema.[38-41] Visual acuity loss may not be as severe in amiodarone-associated optic neuropathy. The median visual acuity for amiodarone-associated optic neuropathy was 20/30 in comparison with NAION at 20/60. However, with NAION, the visual acuity profile was obtained from 420 patients evaluated in the Ischemic Optic Neuropathy Decompression Trial as compared to only 55 patients with amiodarone-associated optic neuropathy. Consequently, the apparent differences in visual acuity may be artifactual, and equivalent visual acuities may be identified as more cases of amiodarone-associated optic neuropathy are reported.[41] Visual field loss in amiodarone-associated optic neuropathy is similar to that observed in NAION; the characteristic visual field defect being an arcuate or

altitudinal scotoma, but other patterns, such as constriction or central scotomas, may be noted.

The proportion of patients having improved, stable, or worsened visual acuity on follow-up and the relative permanency of visual field loss in amiodarone-associated optic neuropathy are similar to that observed in natural history and control populations of patients with NAION.[39,41] That amiodarone-associated optic neuropathy could appear similar to NAION raises the specter that amiodarone-associated optic neuropathy is, in reality, NAION, which may occur with higher frequency among patients with cardiac arrhythmias. Patients who require amiodarone therapy frequently have similar risk factors as patients with NAION. Risk factors for NAION include a previous attack of NAION in one eye, sleep apnea (odds ratio 11.2), small optic nerve cup-disc ratio (odds ratio 8.0), age greater than 50 years (odds ratio 4.6), HLA-A29 antigen (odds ratio 4.6), chlamydia pneumonia (odds ratio 3.5), diabetes mellitus (odds ratio 3.3), oral fever blisters in association with herpes labialis (odds ratio 3.1), and hypertension (odds ratio 1.8).[27,52-63] However, to our knowledge, no study has shown that cardiac arrhythmia independently poses a risk factor for NAION.[58] A prospectively designed study in which patients with cardiac arrhythmias are randomized to treatment with and without amiodarone would be needed in order to demonstrate that amiodarone is the cause of the

Table 2. Grouping of the 55 cases of amiodarone-associated optic neuropathy based on the patients' report of visual loss (asymptomatic, unilateral, or bilateral) at presentation as compared with the optic disc edema present (absent, unilateral, or bilateral). Numbers in parentheses represent percent.

Subjective Visual Loss	Unilateral Disc Edema	Bilateral Disc Edema (Simultaneous)	Bilateral Disc Edema (Consecutive)	Retrobulbar Neuropathy (Unilateral)	Retrobulbar Neuropathy (Bilateral)	Total
Asymptomatic	4 (7) Feiner #3,7,8 Gittinger #1	1 (2) Grogan	1 (2) Nagra #1	1 (2) Feiner #13	0	7 (13)
Unilateral (acute)	5 (9) Eryilmaz Feiner #1,2,6 Johnson #2	5 (9) Feiner #4,11 Fikkers Kristin Nazarian	4 (7) Feiner #5 Johnson#1 Palimar Sedwick	1 (2) Johnson #8	0	15 (27)
Unilateral (insidious)	3 (5) Feiner #10 Johnson #7,9	13 (24) Belec Dewachter Ferreiro #1,2 Johnson #3 Krieg Leifert #1,2 Nagra #2,3 Seemongal-Dass Sreih #2 VanZandijcke	1 (2) Uebermuth	0	0	17 (31)
Bilateral (acute)	0	4 (7) Feiner #9,12 Johnson #10 Leifert #3	1 (2) Gittinger #2	0	2 (4) Bartolucci Speicher	7 (13)
Bilateral (insidious)	0	5 (9) Garrett Gobbelé Johnson #6 Polak Sreih #3	0	0	4 (7) Castells Johnson #4,5,11	9 (16)
Total	12 (22)	28 (51)	7 (13)	2 (4)	6 (11)	55 (100)

observed optic neuropathy. Such a study would pose ethical challenges, since amiodarone is generally considered a life-saving intervention.

Clinical patterns suggest that amiodarone-associated optic neuropathy is a real entity, separate from NAION (Table 4). Raised intracranial pressure is a known manifestation of amiodarone-associated optic neuropathy and is not observed with NAION.[64] Additionally, whereas the prevalence of NAION is equally distributed between men and women, men comprised approximately 90% of amiodarone-associated optic neuropathy cases. The higher percentage of men having amiodarone-associated optic neuropathy could reflect reporting bias. It also could be a true disproportionate rate of amiodarone-associated optic neuropathy between men and women. Another possibility is that the difference could be due to the higher rate of cardiac arrhythmias occurring in men with men then receiving more frequent treatment with amiodarone.[47] Unlike NAION which occurs most often in patients with small optic nerve cup-disc ratio, four of five patients with acute visual loss from amiodarone-associated optic neuropathy for whom cup-disc ratio was reported had 0.2 or larger cup-disc ratio.

Another distinguishing feature of amiodarone-associated optic neuropathy is the duration of optic disc edema. Whereas optic disc edema in NAION

Table 3. Classification of the 55 cases of amiodarone-associated optic neuropathy into five categories. The percentages (in parentheses) are based on a denominator of 61 patients as a result of the Feiner's case #5 (Case 7 in this series), Nazarian's case (Case 17), Garrett's case (Case 18), Palimar's case (Case 25), Nagra's case #1 (Case 39), and Grogan's case (Case 44) being counted twice. Palimar's case (Case 25) and Nagra's case (Case 39) had visual loss in the fellow eye after amiodarone was discontinued. Feiner's case #5 (Case 7) had acute visual loss in the right eye, with left eye visual loss occurring one month after amiodarone was discontinued. In retrospect, early fundus photographs of the left eye of Case 7 had shown "minor capillary dilatation and swelling of the disk." The cases by Nazarian, Garrett, and Grogan (Cases 17, 18, 44) had increased intracranial pressure above 200 mmH_2O, but did not satisfy the modified Dandy criteria for pseudotumor cerebri, as the intracranial pressure was less than 250 mmH_2O. With respect to the distribution of optic atrophy, six (33%) were reported for insidious onset group, eight (44%) for the acute onset group, one (6%) for the retrobulbar group, one (6%) for the papilledema group, and two (11%) for the delayed-progressive onset group.

Insidious Onset Optic Neuropathy	Acute Onset Optic Neuropathy	Retrobulbar Optic Neuropathy	Raised Intracranial Pressure/ Pseudotumor Cerebri	Delayed-Progressive Onset Optic Neuropathy
26 (43)	17 (28)	8 (13)	5 (8)	5 (8)
Belec	Eryilmaz	Bartolucci	Fikkers	Feiner #5 [Left]
Dewachter	Feiner #1,2,4,5 [Right],6,9,11,12	Castells	Garrett	Johnson #2
Feiner #3,7,8,10	Gittinger #2	Feiner #13	Grogan	Nagra #1[Left]
Ferreiro #1,2	Johnson #1,10	Johnson #4,5,8,11	Johnson #3	Palimar [Right]
Garrett	Kristin	Speicher	Nazarian	Uebermuth
Gittinger #1	Leifert #3			
Gobbelé	Nazarian			
Grogan	Palimar [Left]			
Johnson #6,7,9	Sedwick			
Krieg				
Leifert #1,2				
Nagra #1[Right],2,3				
Polak				
Seemongal-Dass				
Sreih #2,3				
VanZandijcke				

generally resolves within weeks, the median duration of optic disc edema in amiodarone-associated optic neuropathy was three months. In some cases, the optic disc edema in amiodarone-associated optic neuropathy persisted for eight months. Such a protracted course may not be pathognomonic for amiodarone-associated optic neuropathy. Patients with NAION, particularly those with diabetes mellitus, rarely may exhibit a prolonged course of optic disc edema, sometimes lasting six months to one year.[65] Finally, as indicated by Macaluso et al.,[30] NAION is usually unilateral, whereas amiodarone-associated optic neuropathy often presents as a bilateral and simultaneous optic neuropathy. Nonetheless, our data show that 35% of patients with amiodarone-associated optic neuropathy will present with unilateral optic disc edema.

Several reports have described clinically significant adverse events attributed to amiodarone use, including pulmonary toxicity with chronic cough, pulmonary infiltrates, and fibrosis in 2–17% of patients; thyroid toxicity manifested by clinical hyperthyroidism or hypothyroidism in 2–10% of patients; and hepatic toxicity with liver function abnormalities in 4–25% of patients.[43,47,49,66-69] Neurologic toxicity is common with amiodarone use. Charness et al.[70] observed neurologic side-effects in 54% of 54 patients treated with amiodarone. Symptoms began within one week of treatment in 41% of these individuals. Most patients with neurologic symptoms noted the onset within four months of treatment. Neurologic toxicity was manifested by tremor in 39%, ataxia with staggering gait in 37%, and sensorimotor peripheral neuropathy in 6%, characterized by numbness and tingling of the hands and feet and occasional muscle weakness and atrophy. Sural nerve biopsies have documented loss of large myelinated fibers, clusters of remyelination, and axonal degeneration.[71,72] Numerous intracytoplasmic inclusion bodies were noted in myelinated and unmyelinated fiber Schwann cells, fibroblasts, endothelial and perineural cells.[71-73] In the case by Meier et al.,[72] the iodine content in the nerve and muscle was 40 times higher than in untreated controls. The high iodine content of amiodarone, a di-iodinated benzofuran derivative, is responsible, in part for the thyroid toxicity that occurs with its use.[43,47,67,68] Costa-Jussa and Jacobs,[74] in experimental studies in mice and rats dosed with amiodarone, found lipids accumulated within lysosomes with the formation of intracytoplasmic inclusion bodies in many nervous and non-nervous tissues. In the nervous system, the drug-associated lysosomal inclusions were found in regions without a blood-brain or blood-nerve barrier. Consequently, large accumulations of lysosomal inclusions bodies were present in neuronal, glial, and endothelial cells in areas lacking a vascular barrier, i.e., areas with fenestrated capillaries, such as the area postrema, dorsal root, myenteric plexus, gasserian, and autonomic ganglia.

The toxic reactions associated with amiodarone appear to be related to the unique properties of amiodarone and a class of similar compounds, which includes perhexiline maleate and chloroquine.[75-78] These drugs are cationic compounds with strong amphiphilic properties. They possess hydrophobic features with low water-solubility and simultaneously strong lipophilic characteristics with high affinity for polar lipids. The closely spaced hydrophilic and hydrophobic groups on the amiodarone molecule allow the drug to enter lysosomes and bind irreversibly to polar lipids. Amiodarone is a potent inhibitor of lysosomal phospholipases, resulting in the formation of intracellular drug-lipid complexes that are "nondigestible" and consequently accumulate in lysosomes as intracytoplasmic inclusion bodies.[78] The lamellated or crystalloid patterns of the inclusion

Table 4. Characteristics of Amiodarone-Associated Optic Neuropathy as Compared with Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)

	NAION	Amiodarone Optic Neuropathy
Medication use	Absent	Within 12 months of initiating amiodarone (median: four months)
Gender	Male = Female	Male > Female
Incidence	2.3–10.2 per 100,000 (age >50 years)	~2% (amiodarone users)
Laterality at presentation	Unilateral	Bilateral (65%); unilateral (35%)
Optic nerve cup-disc (C/D) ratio	Small (<0.2)	Any C/D ratio
Increased intracranial pressure	Absent	Occasional
Systemic manifestations	Absent	Tremor, thyroid, pulmonary dysfunction
Duration of disc edema	Within two-to-four weeks	One-to-eight months (median: three months)

bodies depend on the composition of the polar lipids that are deposited. This drug-induced lipidosis has attendant consequences of a generalized lysosomal storage disorder similar to Fabry's disease.[1,2,79-82] This latter disorder is an X-linked recessive disease due to mutations in the gene encoding the lysosomal enzyme alpha-galactosidase A.[83] As a result, there is systemic accumulation of incompletely metabolized glycosphingolipids, primarily globotriaosylceramide, producing cardiac, renal, and neurologic disorders.[80,81]

The exact mechanism of cellular toxicity of amiodarone and its major metabolite, desethylamiodarone, is uncertain.[84] Mansour et al.[85] documented selective accumulation of intracytoplasmic lamellar inclusions in large axons of the optic nerve in a patient who had taken amiodarone, 400 mg every other day, but did not have evidence of optic neuropathy. Garrett et al.[7] postulated that amiodarone freely permeates the fenestrated capillaries of the adjacent peripapillary choroid, reaching the prelaminar optic nerve through the border tissue of Elschnig. Lamellar inclusions then accumulate in glial cells, producing swelling of these cells, secondary axonal compression, blockage of axoplasmic flow, and optic neuropathy with optic disc swelling.[7] Although this mechanical model for optic neuropathy is possible, a biochemical dysfunction inducing optic neuropathy appears more plausible. A biochemical pathogenesis in part could involve free radicals.[86-88] Amiodarone is known to generate oxygen-free radicals when the amiodarone molecule is chemically reduced and iodine is cleaved from the amiodarone molecule.[86] In addition to the increased concentration of iodine in tissues, the amiodarone generated free radicals cause an increase in cellular lipid peroxidation and drug-lipid inclusions.[86] It remains uncertain whether these drug-lipid inclusions found in retinal ganglion cells interfere with axoplasmic transport causing optic disc edema and optic nerve dysfunction.[1]

In summary, we have classified amiodarone-associated optic neuropathy into five categories based on temporal characteristics and optic nerve appearance: insidious-onset (43%); acute-onset (28%); retrobulbar (13%), increased intracranial pressure (8%), and delayed-progressive onset (8%). Although overlap in clinical presentation with NAION does occur, in some cases, amiodarone-associated optic neuropathy is distinguishable from NAION. Clinical manifestations commence within 12 months of the start of therapy for almost 90% of patients, and the median interval between initiation of therapy and the onset of vision loss is four months. Over 10% of patients with amiodarone-associated optic neuropathy may be asymptomatic, despite the presence of optic neuropathy. For these reasons, it may be prudent to have patients who have been prescribed amiodarone undergo ophthalmologic examination at baseline and at four, eight, and 12 months after initiating therapy. Subsequently, annual ophthalmologic visits may suffice. Clinicians are aware of the vortex-like corneal epithelial disorder associated with amiodarone use.[43,66-68] This corneal verticillata, first described by François in 1968,[89] is the hallmark of amiodarone keratopathy and is often present within six- to 12 months of amiodarone use.[79,90] The keratopathy is dose- and duration-dependent, accounting for its variable occurrence in 76–100% of amiodarone treated cases.[79,90] Consequently, patients with amiodarone-associated optic neuropathy may *not* exhibit corneal verticillata, particularly since the median duration of amiodarone use in patients with vision loss is four months. Hence, absence of amiodarone keratopathy should not dissuade clinicians from establishing the diagnosis of amiodarone-associated optic neuropathy. Although in most cases the vision loss remains unchanged, it is possible that early detection and discontinuation of amiodarone could make a difference in the visual prognosis. Ghosh and McCulloch[1] in 1984 asked, "Would a higher dose of amiodarone [greater than 600–1,200 mg daily] and a longer duration of therapy [greater than 18–30 months] cause more ganglion cells to be affected and perhaps produce irreversible visual damage?" The answer to this conundrum is, "Yes, optic neuropathy with irreversible visual loss can occur. It happens even with standard doses of 200 mg and 400 mg daily and with median time of onset being four months."

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