ORIGINAL ARTICLE

Amiodarone-associated Optic Neuropathy—A Clinical Criteria-based Diagnosis?

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ABSTRACT

Amiodarone-associated optic neuropathy (AAON) is a controversial diagnosis with possible impact on vital cardiac therapy decisions. This retrospective case series aims for application of distinguishing features of AAON versus non-arteritic ischaemic optic neuropathy (NAION): Bilaterality, mode of onset, degree of optic nerve dysfunction, structure of uninvolved disc (unilateral cases), and systemic toxic effects. Applying these criteria to patients with disc swelling under amiodarone, the authors identified four unilateral disc swellings, one with NAION-typical features only and three with one or more NAION-atypical features. All three sequential and six bilateral cases showed one or more NAION-atypical features. The 12 cases highlight the persisting diagnostic dilemma arising from diversity of presentation, lack of plausible pathomechanism, and controversial existence of the entity itself.

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Introduction

Amiodarone is a widely used anti-arrhythmic drug, which significantly lowers mortality of sudden cardiac death.^{1,2} Bioavailability after oral intake varies between 30% and 80%. It accumulates in various organs and tissues of the body. Therapeutic levels of amiodarone are usually reached within a week; half-life is 20–100 days.^{3–5}

Well-known side effects of amiodarone are prolongation of QT interval, bradycardia, thyroid dysfunction, interstitial pneumonitis, metallic taste, nausea, and liver toxicity. Vortex keratopathy is almost pathognomonic.⁵ Several case reports describe optic neuropathy possibly related to amiodarone.^{6–18} One pathophysiologic theory of damage is mechanical or biochemical decrease of axoplasmic flow due to deposition of lamellar bodies within optic nerve axons.³ Experimental studies suggest potential neurotoxic effect of amiodarone,^{19–23} and in 2016, a novel potential pathomechanism was reported by Liao et al.²⁴ This study showed that amiodarone induced apoptosis of RGC-5 cells (a clonal, retinal, neuronal cell line, established as a model to study glaucomatous damage in vitro) via

inhibiting the phosphoinositide 3-kinase (PI3K)/Akt/FoxO3a pathway. However, overall, it is still controversial whether amiodarone-associated optic neuropathy (AAON) is a mere drug related condition or whether it represents a form of non-arteritic ischaemic neuropathy (NAION) in a high-risk cardiovascular population.^{3,4,25–32} Macaluso et al. proposed several distinguishing features of AAON versus NAION, with the suggested hallmarks of AAON being insidious onset, slow progression, bilateral visual loss, and protracted disc swelling.³³ In 2006, Purvin et al. refined the diagnostic criteria by including a broader spectrum of clinical features: bilaterality, mode of onset, degree of optic nerve dysfunction (mild degree defined as visual acuity of $\geq 20/40$ and relative afferent pupillary defect [RAPD] of ≤ 0.9 log units), structure of uninvolved disc in unilateral cases, and systemic toxic effects.³⁴ The purpose of this retrospective chart review is the application of these criteria to clinical cases to confirm the previously described differentiating features and to discuss the persisting controversy of AAON given its clinical diversity of presentation.

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Materials and methods

We performed a retrospective chart review of patients examined at the University Hospital Zurich with the diagnosis of possible AAON from 1995 to 2014. Included were patients >18 years who developed an optic neuropathy under amiodarone therapy. Cases with missing information about amiodarone therapy and cases suspected of having an optic neuropathy due to another pathology were excluded.

The following data were reviewed from patients records: amiodarone therapy (indication, dosage, duration, cumulative dose until first symptom), co-morbidities, co-medication, age at diagnosis of optic neuropathy, clinical findings (visual acuity, relative afferent pupillary defect, disc appearance including cup/disc ratio) at presentation and follow-up, laterality, length of interval in case of sequential incidence, and visual fields.

The cases were divided in groups according to the criteria proposed by Purvin et al., i.e., bilateral disc swelling, unilateral disc swelling with NAION-typical features, and unilateral disc swelling with atypical features (mode of onset, degree of optic nerve dysfunction, structure of uninvolved disc, and systemic toxic effects).³⁴ Additionally, we identified a fourth group that presented with sequential disc swelling. Data were coded in Excel (Microsoft Office Excel 2007; Microsoft Corporation, Redmond, WA, USA) and used for descriptive statistics.

This study was approved by the cantonal ethical committee of Zurich (KEK-ZH 2014-0593).

Results

Thirteen patients with optic neuropathy and amiodarone therapy were identified from 1995 to 2015 (mean age 71 years $\pm$ 7.0 [SD]; 2 female). Their clinical data are summarised in Table 1. Amiodarone dosage was 1 g/week in 1 case, 1.4 g/week in 10 cases, and 3 g cumulative intravenous in 1 case. The intravenous administration was due to a postinterventional atrial fibrillation after cardiac bypass surgery.³⁵ In one case, no reliable dosage for amiodarone was documented. The indication for amiodarone was ventricular or supraventricular arrhythmia in all cases. There were no

reports of systemic symptoms consistent with amiodarone toxicity, especially no dyspnoea/cough or gastrointestinal symptoms (nausea, emesis, metallic taste).

Data of the three unilateral cases with NAION-atypical features are summarised in Table 1. Cases 1 to 3 had one atypical sign for NAION, with visual acuities (VAs) of 20/20, 20/40, and 20/30.

Data of the one unilateral case (case 4) showing no atypical sign is shown in Table 2. Data of the three sequential patients are shown in Table 3. Case 11 showed one atypical sign for NAION with an insidious beginning of symptoms, case 12 demonstrated three atypical signs with an insidious onset, a relatively preserved optic nerve function (VA 20/20, no RAPD), and a cup/disc ratio of 0.3 of the fellow eye. Case 13 also showed one atypical NAION sign with a VA of 20/25 and no RAPD. Resolution of disc swellings were prolonged where documented. Figures 1 and 2 show the clinical findings of patient 12.

Data of the six bilateral cases are shown in Table 4. Apart from the bilaterality, all cases showed one or more additional atypical signs for NAION. Four out of six showed an insidious onset, and five out of six at least in one eye a visual acuity of $\geq$ 20/40. Optic disc swelling was protracted in half of the cases. Figures 3 and 4 show the clinical findings of patient 6.

Discussion

Amiodarone-associated optic neuropathy is still a controversial entity. Its underlying pathomechanism remains unclear, although ultrastructural changes within optic nerve axons with possible (bio-)mechanical disturbance of axoplasmic flow have been described, and recently, another pathway of retinal neuronal cell damage (PI3K/Akt/FoxO3 inhibition) has been postulated.^{3,24} In 2007, Mindel et. al. could not find bilateral vision loss being related to amiodarone treatment in a prospective, controlled, double-masked study with over 1600 patients.²⁸ Ophthalmologic examinations were not performed, albeit there was not one report of bilateral vision loss over the minimal observation time of 27 months. So far, this is the only study trying to describe AAON as a separate entity in a systematic prospective way. Initially

Table 1. Unilateral disc swelling, 1+ atypical NAION findings: Distinguishing criteria for amiodarone-associated optic neuropathy versus non-arteritic anterior ischaemic neuropathy.

Case	Age at presentation /gender (F/M)	Laterality	Onset sudden vs. insidious	Amiodarone dosage mg/week	Cumulative dosage (g) until symptoms	VA involved eye	VA after 3 months involved eye	VF involved eye	RAPD involved eye	CDR fellow eye	Systemic toxic effects	Time to resolution of swelling (weeks)	Co-medication
1	68 /M	Unilateral R	Sudden	1400	146	20/20	Not documented	R altitudinal inferior	Yes	0	None	Not documented	Ticlopidine
2	65 /M	Unilateral R	Unknown	1400	Unknown	20/40	20/30	R altitudinal inferior	Yes	0.1	None	Not documented	Phenprocoumon, ramipril, bisoprolol and thiazide, spironolactone
3	85 /F	Unilateral L	Sudden	1400	>56	20/30	Not documented	L objective: none L subjective: inferior altitudinal	Yes	0.1	None	Not documented	Enalapril, amlodipine, torasemide, atorvastatin, metformin, phenprocoumon, nitroglycerin-patch, cyanocobalamin depot, metoprolol and hydrochlorothiazide

Note. VA = visual acuity; RAPD = relative afferent pupillary defect; CDR = cup/disc ratio; R = right eye; L = left eye. Bold values = atypical for NAION.

Table 2. Unilateral disc swelling, no atypical finding for NAION: Distinguishing criteria for amiodarone-associated optic neuropathy versus non-arteritic anterior ischaemic neuropathy.

Case	Age at presentation /gender (F/M)	Laterality	Onset sudden vs. insidious	Amiodarone dosage mg/week	Cumulative dosage (g) until symptoms	VA involved eye	VA after 3 months involved eye	VF involved eye	RAPD involved eye	CDR fellow eye	Systemic toxic effects	Time to resolution of swelling (weeks)	Co-medication
4	79 /M	Unilateral L	Sudden	1400	>48	Light perception	Not documented	L central scotoma	Yes	0	None	Not documented	Rivaroxaban, levocetirizine, torasemide, zolpidem, losartan, bisoprolol and thiazide, spironolactone, ropinirole, levothyroxine-natrium

Note. VA = visual acuity; RAPD = relative afferent pupillary defect; CDR = cup/disc ratio; L = left eye.

Table 3. Sequential disc swelling: Distinguishing criteria for amiodarone-associated optic neuropathy versus non-arteritic anterior ischaemic neuropathy.

Case Nr.	Age at presentation / gender (F/M)	Laterality (first eye / second eye)	Onset sudden vs. insidious	Amiodarone dosage mg/week	Cumulative dosage (g) until symptoms	Interval to involvement of 2nd eye (weeks)	VA 1° involved eye	VA after 3 months 1° involved eye	VA 2° involved eye at involvement	VF 1° involved eye	VF 2° involved eye at involvement	RAPD 1° involved eye	CDR fellow eye at first eye involvement	Systemic toxic effects	Time to resolution of swelling 1°/2° (weeks)	Co-medication
11	75 / M	sequential (L/R)	insidious	1000	unknown	48	unknown	unknown	20/200	normal	normal	unknown	0	none	not documented	Metoprolol& Hydrochlorothiazide, Isosorbide Dinitrate
12	75 / M	sequential (L/R)	insidious	1400	14	18	20/20	20/20	finger counting at 1 meter	superior altitudinal defect	superior altitudinal defect	No	0.3	none	18 / not documented	Metoprolol& Hydrochlorothiazide, Allopurinol, Enalapril, Phenprocoumon
13	71 / M	sequential (R/L)	sudden	1400	unknown	3	20/25	20/30	20/50	quadrant defect superonasal	quadrant defect inferonasal	No	0.1	none	15/15	Acetylsalicylic acid, Phenprocoumon, Losartan 100 mg, Pantoprazole

Note. VA = visual acuity; RAPD = relative afferent pupillary defect; CDR = cup/disc ratio; R = right eye; L = left eye; 1° = primary; 2° = secondary. Bold values = atypical for NAION.

Figure 1. Documentation of case 12, sequential disc swelling. (A) Fundus photography of left disc swelling at initial presentation (1° involved eye). (B) Fundus photography at interval of involvement of second eye, 18 weeks after initial presentation. Left disc pallor and right disc swelling with haemorrhages.

Figure 2. Documentation of case 12, sequential disc swelling. (A) Goldmann visual fields of superior altitudinal defect left eye at initial presentation. (B) Goldmann visual fields of superior altitudinal defects both eyes at interval of involvement of second eye.

Table 4. Bilateral disc swelling: Distinguishing criteria for amiodarone-associated optic neuropathy versus non-arteritic anterior ischaemic neuropathy.

Case	Age at presentation / gender (F/M)	Laterality	Onset sudden vs. insidious	Amiodarone dosage mg/week	Cumulative dosage (g) until symptoms	VA R / L	VA after 3 months R / L	VF	Systemic toxic effects	Co-medication
5	76 / F	Bilateral	Insidious	1400	16.8	20/40 / 20/200	20/200 / 20/200	R > L concentric narrowing	None	Irbesartan, carvedilol, spironolactone
6	65 / M	Bilateral	Sudden	Inconclusive	50	20/20 / 20/25	20/200 / 20/400	R/L superior altitudinal defects	None	Acetylsalicylic acid, atenolol
7	60 / M	Bilateral	Insidious	1400	43.4	20/20 / 20/25	Not documented	R/L altitudinal superior defects	None	Valsartan 160 mg/day, amlodipine 10 mg/day
8	64 / M	Bilateral	Sudden	3000 (i.v.)	3	20/25 / 20/60	20/25 / 20/30	R circular narrowing L superior and inferonasal defect	None	Pantoprazole, acetylsalicylic acid, nifedipine, clopidogrel
9	75 / M	Bilateral	Insidious	1400	4.2	20/60 / 20/200	Not documented	R/L central scotomas	None	None
10	70 / M	Bilateral	Insidious	1400	Unknown	20/25 / 20/30	Not documented	R/L concentric narrowing	None	Acetylsalicylic acid, lisinopril

Note. VA = visual acuity; R = right eye; L = left eye.

characterised as a bilateral mild optic neuropathy with slow progression, AAON has been recognised to be more variable, since also unilateral cases, cases of sudden, profound vision loss, and cases with fast progression have been described.^{3,4,25,26,28,33,34,36}

The proposed mechanical or biochemical toxicity as a systemic adverse event seems to be consistent with bilateral onset of optic neuropathy, and generally, bilateral neuropathies under amiodarone therapy are considered AAONs. However, with its postulated variety of presentation, a distinction between a simultaneous bilateral NAION and AAON seems very difficult or even impossible. For unilateral cases, there is no theory explaining and proving unilateral optic neuropathy as consequence of systemic drug toxicity. Among our patients, patient 4 showed all features of a typical NAION, whereas cases 1 to 3 had atypically preserved optic nerve function. Is one atypical feature sufficient to consider amiodarone as the causative agent instead of simple ischaemia? Does the anatomy of the optic canal or the optic disc alter mechanical properties or is there an imbalance in vascular regulation or vessel distribution predisposing to unilateral damage by amiodarone? Should amiodarone treatment be continued in case of typical unilateral NAION presentation?

One subgroup emerging in this study is the group of patients showing “sequential” disc swellings. Incidence of sequential NAION is variable from 11% to 73%.^{36,37} Again, all of our sequential cases showed one or more features described as atypical for NAION. Can sequential presentation of AAON be explained? As mentioned before, there could be different variables causing altered vulnerability of the two optic nerves in a same patient. Especially short time intervals could be explained by earlier or later accumulation of a critical level of axonal damage. As an example, Leber’s hereditary optic neuropathy (LHON) is another entity in which the breakdown of optic nerve function occurs in a sequential manner despite a genetic predisposition. Is there a cut-off in time from bilateral to (pseudo-) sequential? To the best of our knowledge, there are no studies addressing possible distinctive features of sequential incidence that consider variables such as time interval.

Figure 3. Documentation of case 6, bilateral disc swelling. (A) Slit-lamp photography of cornea verticillata both eyes. (B) Fundus photography of bilateral disc swelling with haemorrhages at presentation.

Figure 4. Documentation of case 6, bilateral disc swelling. Goldmann visual fields of bilateral superior altitudinal defects.

The limitations of this study are its retrospective design with missing data in some cases and the small number of included patients due to the low incidence of this condition.

Several postulated features might be helpful to distinguish between AAON and NAION. Applying such criteria in a retrospective manner does not necessarily lead to certainty of diagnosis. In the context of overlapping clinical features with NAION, one still encounters difficulty in diagnosing AAON, especially as long as we lack comprehensible pathomechanisms for AAON.

As long as neither existence of AAON nor reliable definite criteria of differentiation between AAON and NAION are evidenced, a very cautious approach seems to be advisable. Amiodarone treatment needs to be actively assessed in patients with optic neuropathy, and immediate consultation with the cardiologist is necessary if optic neuropathy occurs under amiodarone treatment. In doubt, amiodarone treatment should be stopped if there is an alternative solution to control arrhythmia. Regular ophthalmologic screening has been discussed, but with

lacking evidence, recommendations about frequency and start of such a screening are difficult to make.^{3,25,26}

Further research about possible pathophysiology and prospective studies about incidence and characteristics of optic neuropathies under amiodarone would be helpful to shed light on AAON.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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