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# AMIODARONE-INDUCED ATAXIA: A CASE REPORT OF SEVERE CEREBELLAR DYSFUNCTION AND REVIEW OF LITERATURE

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**Abstract:** Amiodarone therapy is widely prescribed in patients with atrial fibrillation. The higher prevalence of this arrhythmic heart disease, and the specific age-related issues of homeostasis in the elderly population, makes this group particularly exposed to its adverse effects. Among the many described side-effects, neurological impairments are the less documented and studied. Because amiodarone can be responsible for severe complications, as described in the case below, a close monitoring is necessary throughout its prescription. Awareness should be brought on the amiodarone-induced neurological side-effects as they could be overlooked.

**Key words:** Amiodarone, ataxia, elderly, side-effects.

## Introduction

Amiodarone, a class III antiarrhythmic agent, is one of the most prescribed antiarrhythmic drugs in patients with atrial fibrillation to maintain a sinus rhythm. Because of its numerous extracardiac side effects, it makes it a secondary-line treatment in the rhythm control strategy by the European Society of Cardiology (1). Still, it remains commonly used in the elderly population due to prevalence of atrial fibrillation. If side effects such as thyroid dysfunction, skin alteration or lung

damage are well-known, there is a need to increase awareness on neurological adverse events, infrequent, probably under-reported, and many times overlooked. We present an interesting case of early severe amiodarone induced-cerebellar syndrome of an 85 year-old (yo) man.

## Case report

An 85-yo man, active and fully-autonomous, reported clinical picture of balance disorders, vertigo and dysarthria

**Table 1**  
Radiological examination

Radiological additional examinations	Results
Cerebral CT angiography	No arguments for recent ischemic or haemorrhagic stroke No occlusion of the supra-aortic vessels
Brain MRI (repeated 3 weeks later)	Numerous non-confluent periventricular and deep white matter hyperintensities suggesting vascular process (small vessel disease) Small right parieto-occipital ischemic sequelae Age-related diffuse cortical and subcortical atrophy No meningeal lesion No evolving lesion
Medullary MRI	Degenerative disc disease No abnormal intracanal contrast-enhancement
Thoraco-abdominal and pelvis CT scan (repeated 1 month later)	Unremarkable No evolving lesion
18F-FDG PET scan	Focal intense hypermetabolism in the second part of the duodenum
Upper gastrointestinal endoscopy	No endoscopic argument for hypermetabolism of the duodenum Discreet duodenal mucosa inflammation without histological change after anathomopathological analysis
[123I]FP-CIT (DaTSCAN) scintigraphy	No arguments for typical dopaminergic pathways damage (normal striatal fixation of the radioligand based on visual assessment)

CT: computerized tomography; MRI: magnetic resonance imaging; 18F-FDG PET scan: positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro- D-glucose; [123I]-FP-CIT scintigraphy: (123)

**Table 2**  
 biological and others additional examinations

Biological and others additional examinations	Results
Blood tests	No inflammatory syndrome Normal liver, renal and thyroid functions Monoclonal peak in the gamma zone (kappa IgG) on serum electrophoresis No systemic diseases antibodies (anti-ENA, anti-ANA) No anti-transglutaminase antibodies No antineuronal antibodies with intracellular and cell surface target No antibodies of the neuromuscular junction Negative serology for HIV, HBV, HCV and <i>Borrelia burgdorferi</i> No cryptococcal antibodies Negative screening for Whipple disease Low lead level Vitamin B6, C and E deficiencies, correct B1 and B12 levels
Cerebrospinal fluid	Clear, no inflammatory Bacteriological, virological and mycological negative culture Normal Alzheimer's disease biomarkers (Tau, p-Tau, A $\beta$ 42) No antineuronal antibodies No cryptococcal antigen Monoclonal immunoglobulin bands (IgG)
Myelogram with immunophenotyping	No arguments for multiple myeloma or lymphoma Clonal B-lymphocyte population compatible with Waldenström's disease invalidated with negative MYD88 L265P mutation

HIV: Human Immunodeficiency virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus

for three weeks. His past medical history highlighted cardiovascular risk factors (age, hypercholesterolemia and arterial hypertension), an ischemic stroke without consequences and a diagnosis of atrial fibrillation with rhythm control therapy by amiodarone (200mg per day) only 3 weeks before the onset of symptoms. He had no acute or chronic use of alcohol and no family background of neurological disorders. A rapid deterioration with cerebellar ataxia brought him to the emergency room where brain imaging was first performed and eliminated recurrent stroke (table 1). In the following weeks, neurological symptoms kept worsening with evident cerebellar syndrome (severe ataxia, axial hypotonia, hypermetria), associated with dysarthria (reduction in the intelligibility) and major dysphagia (oropharyngeal desynchronization with aspiration issues). He had neither vibratory or sensory disturbance, nor vestibular symptoms suggesting others aetiologies to the ataxia. The patient underwent multiple laboratory testings and radiological investigations (table 1 and 2) but none of them showed significant abnormalities ruling out the main etiological hypotheses: vascular, auto-immune, infectious, neoplastic, paraneoplastic, deficiency or neurodegenerative. We only noticed a low level of vitamin E (4.77mg/l; normal: 9,5-18mg/l) but not associated with

malabsorption lipid diseases or arguments for a genetic cause to the deficit. We also took note of incidental finding of clonal-lymphocyte B population without significant clinical outcome in the view of haematologists. A corticosteroid therapy had been started as a trial treatment in the absence of diagnosis, without unfortunately any improvement observed on the symptoms.

Potential amiodarone-related iatrogenia had been discussed only 2 months after admission, resulting in drug discontinuation. At this point, the patient was in a critical clinical situation with walking inability, nutritional support through gastrostomy and need of permanent assistance for everyday living. In the ensuing days, we first observed an interruption of symptom-deterioration. Within 3 weeks, following an intensive rehabilitation program, we noticed a progressive recovery with significant clinical improvement, on the dysarthria first, then on the dysphagia and the cerebellar ataxia. Concerning dysphagia, objective data with video recordings of the functional assessment of deglutition performed before discontinuation confirmed the clinical observations: desynchronization of the oropharyngeal phase with penetration, major stasis of yogurt during swallowing test and presence of saliva on the larynx. Three months after drug

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discontinuation, no penetration or stasis were observed during the same test by FEES (Fiberoptic endoscopic evaluation of swallowing). Two months after amiodarone had been stopped, the patient was still inwards, following a rehabilitation program with continuous progress. He was able to walk with aid of a walker and kept gaining autonomy for activities of daily living. Finally, the patient was discharged to his previous residential facility, 4 months after amiodarone discontinuation. Complete recovery was observed for ataxia, dysarthria, dysphagia, and activities of daily living. Sarcopenia persisted due to the intense initial loss of muscle mass. Due to this fact a walking aid was necessary at discharge.

### Discussion

As previously said, neurological toxicity due to amiodarone therapy remains insufficiently known among the medical community. This issue was highlighted in this case report as the diagnosis of amiodarone-induced neurological toxicity was finally evoked after 2 months of intense medical investigation. Neurological manifestations cover a wide spectrum with various prevalences. According to the French national pharmacovigilance, tremor or peripheral neuropathy (classically described as a demyelinating sensorimotor polyneuropathy responsible for proprioceptive disturbance, sometimes associated with myopathy (2)) are frequently reported ( $\geq 1\%$  to  $10\%$ ) but cerebellar ataxia and cognitive impairment are very infrequent ( $< 0.01\%$ ) (3).

Physiopathology of amiodarone toxicity isn't well-established for now. The main assumption is based on amiodarone and mono-N-desethylamiodarone (its major oxidative metabolite) ability to inhibit almost completely phospholipid (PL) degradation by liposomal phospholipases, leading to PL accumulation with liposomal inclusion in tissues such as lungs or brain (as the blood-brain barrier allows the passage of low levels of amiodarone) (4, 5). Hypothesis about formation of stable and non-degradable amiodarone-PL complexes could also participate (4, 10).

Several studies have underlined length of time as the leading risk factor for amiodarone neurotoxicity (Orr et al 2009 (6), Pomonio et al 2015 (4)). In scientific literature, cases of neurological disorders induced by amiodarone reported variable delay between treatment initiation and the start of symptoms for common dosage (average of 200mg to 400mg per day): from a month (Chaubey et al 2013 (7)) to 8 months (Indle et al 2008 (8), Crauser et al 2005 (9)).

In our case, we can be concerned by the rapid onset of symptoms. Knowing toxicity mechanism of amiodarone, we could think of a relation with low blood level of vitamin E. Indeed, alpha-tocopherol has a role of stabilising cell membranes by binding phospholipase hydrolysis products, restoring membrane fluidity and complexing with free fatty acid. Honegger et al (10) highlighted an interference between alpha-tocopherol and amiodarone-PL complexes that would reduce drug accumulation and restore PL catabolism. Looking for vitamin E deficiency in patients with amiodarone adverse events could be an option to a better understanding of their occurrence.

In conclusion, because of the possible severity of extracardiac side effects of amiodarone, worsened by the drug's long half-life due to high potential for bioaccumulation in lipid-rich tissues, monitoring its prescription is much needed to prevent critical situation, especially in elderly population. Wider recognition of this syndrome may avoid neurological impairments that could eventually be irreversible.

*Conflict of interest:* The authors report no conflicts of interest.

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