CASE REPORT

Ataxia: a diagnostic perplexity and management dilemma

Vinod K Chaubey,¹ Lovely Chhabra,² Aaysha Kapila³¹Department of Internal Medicine, Saint Vincent Hospital, University of Massachusetts Medical School, Worcester, Massachusetts, USA²Department of Internal Medicine, Saint Vincent Hospital, University of Massachusetts Medical School, Worcester, Massachusetts, USA³Department of Internal Medicine, East Tennessee State University, Johnson City, Tennessee, USA**Correspondence to**Dr Lovely Chhabra,
lovids@hotmail.com**SUMMARY**

A 79-year-old woman presented with lower extremity weakness and unsteadiness for 2 weeks. She was recently diagnosed with refractory atrial flutter and was prescribed amiodarone. Physical examination revealed signs of cerebellar dysfunction. Neuroimaging including CT and MRI were unremarkable. Her hospital course included the development of ventricular tachycardia necessitating increment in amiodarone dose. Laboratory studies were unremarkable except mild transaminitis. Other workup including the one for paraneoplastic neurological involvement was negative. The patient experienced worsening of ataxia requiring assistance with ambulation. In view of comprehensive routine negative work-up for ataxia, recent use of amiodarone and worsening of symptomatology with increase in its dosing, drug-induced neurotoxicity from amiodarone was suspected. Amiodarone dose was subsequently reduced and mexilitine was introduced as an additive antiarrhythmic therapy for ventricular tachycardia. In follow-up, the patient experienced significant improvement in her symptoms and was able to ambulate independently. She was subsequently discharged to short-term rehabilitation.

BACKGROUND

Amiodarone is a panache drug and corner stone for the medical management of a variety of supraventricular and ventricular tachycardias. Though side effects of amiodarone use on the lung, thyroid, liver and eye function are well known, its neurotoxic side effects remain underappreciated. Amiodarone-induced ataxia from cerebellar toxicity and peripheral neuropathy has been previously reported. Despite a previously well-described neurotoxicity of amiodarone, its awareness among internists and even specialists remains underperceived. The physician's predicament arises when amiodarone use is warranted for the management of life-threatening arrhythmias despite the presence of amiodarone-related neurotoxicity. In this report we present an interesting case which highlights the significance of considering amiodarone as a cause of neurotoxicity and also provides a plausible management approach for the clinical scenario when the use of antiarrhythmic therapy is unavoidable despite its toxic effects.

CASE PRESENTATION

A 79-year-old woman presented to the emergency department with lower extremity weakness and unsteadiness. Further history revealed progressive generalised weakness and lethargy for 2 weeks. She

denied any light headedness or dizziness. At her baseline, she was independent of daily living activities and could ambulate using a walker. There was no history of head trauma, fall, fever or any viral prodromal symptoms in the past.

Medical history included coronary artery disease and ischaemic cardiomyopathy with biventricular automated internal cardiac defibrillator. Social history was negative for smoking, alcohol use or illicit-drug use. She was admitted 4 weeks prior for refractory atrial flutter and was discharged on oral amiodarone 400 mg twice daily after she had received initial intravenous amiodarone therapy. Amiodarone dose was subsequently tapered to 200 mg twice daily after outpatient cardiology follow-up 2 weeks earlier and this was conducted due to associated drug side effects, mainly paraesthesias.

During the current presentation, she had ventricular tachycardia and hence, the dose of amiodarone was increased to 400 mg twice a day. During the hospital course, her ataxia worsened significantly.

Her initial vital signs were stable. She was alert and oriented to time, place and person. Cardiopulmonary examination was normal. Neurological examination was positive for finger-to-nose point testing, truncal instability, bilateral heel-shin ataxia, diminished ankle jerks and bilateral up-going plantar reflexes. Her joint position sense and pinprick were preserved but vibration sense was equivocal. She clearly had an unsteady gait due to imbalance. She required assistance for transfer from bed to walker. The motor power when tested in supine resting position appeared normal.

INVESTIGATIONS

Initial basic laboratory studies including haemogram and basic metabolic panel were unremarkable, except mild eosinophilia (10%). Liver function tests revealed mildly elevated aspartate aminotransferase (52 IU/L) and alanine transaminase (67 IU/L). Thyroid function tests were within reference range. Urinary analysis was unremarkable. CT scan of the brain was largely unremarkable except age-related atrophic changes. MRI and MR angiography of the brain were unremarkable except an old small left-lacunar infarct. Amiodarone level was 1.4 µg/mL, desethylamiodarone level was 1.6 µg/mL and digoxin level was 0.7 ng/mL. Workup for anti-Ro, anti-La, anti-Hu antibodies and rapid plasma reagin was negative. Vitamin B₁₂ level was normal (840 pg/mL).

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DIFFERENTIAL DIAGNOSIS

- ▶ Posterior circulation stroke
- ▶ Paraneoplastic cerebellar degeneration
- ▶ Drug-induced ataxia
- ▶ Sensory ataxia
- ▶ Spinocerebellar ataxia
- ▶ Subacute combined degeneration

TREATMENT

In view of recent history of amiodarone use, abnormal liver function test, eosinophilia and other negative neurological workup, drug-induced neurotoxicity was suspected. To achieve sustained remission into sinus rhythm, mexilitine 150 mg twice daily was added to the current regimen.

Amiodarone dose was gradually tapered to 100 mg twice daily and mexilitine 150 mg twice daily was continued.

OUTCOME AND FOLLOW-UP

After 1 week of new drug regimen, patient's cerebellar symptoms significantly improved. She was discharged to short-term rehabilitation with a plan for outpatient follow-up.

DISCUSSION

The neurological side effects of amiodarone are myriad including tremor, peripheral sensorimotor neuropathy, ataxia, insomnia, cognitive impairment and Parkinson's disease. The major risk factors in amiodarone-induced toxicity are the duration of therapy and dosing. Neurological side effects are often dose related and are less likely in the lower dose range usually used in clinical practice. Age, sex and indication for therapy do not seem to affect amiodarone-related neurotoxicity.¹ The incidence of amiodarone-induced neurotoxicity in general ranges from 2.8% to 74%.²⁻³ All above neurological side effects are underappreciated and rarely becomes part of differential diagnostic algorithm in day-to-day clinical practice. This is understandable because of wide spectrum of neurological effects of amiodarone which could pose a diagnostic challenge not only for internist but also for neurologist. Since neurotoxicity is much less talked about among the various side effects of amiodarone, there is no consensus guideline screening and monitoring for the amiodarone-induced neurotoxicity unlike pulmonary function or thyroid function tests for lung and thyroid dysfunction, respectively.

The precise mechanism of amiodarone-induced neurotoxicity is unknown, but may be explained by penetration of amiodarone into nerve tissue and induction of neuropilipidosis. The membrane permeability is altered so that amiodarone can accumulate within membrane-surrounded lysosomal structures or inclusion bodies. Under microscopy, the nerve biopsies have shown lipid-inclusion bodies within the Schwann cell. These lysosomal inclusions are believed to contain amiodarone. In experimental studies, sural nerve biopsies did reveal mild demyelination and many inclusion bodies in the axoplasm and in Schwann cell cytoplasm.⁴⁻⁵

Amiodarone-induced ataxia is one of the commonest side effects among the all the neurotoxic side effects and is quite disabling. Ataxia is worrisome because it increases the risk of fall-related morbidity especially in the elderly. Significantly, the incidence of ataxia in particular is quite variable with incidence as low as 7% to as high as 37% as reported by prior studies.⁶⁻¹⁰

The crucial management dilemma arises when amiodarone remains part of differential diagnosis of ataxia in a patient where there is compelling indication for having the patient to

be continued on amiodarone. In general, amiodarone is usually started for arrhythmia when other treatments are not an option or have failed. Thus, discontinuation of the drug could be detrimental or life-threatening. Probably, a logical option in such a scenario is to add a new antiarrhythmic drug with intention to reduce the dose-related neurotoxicity of amiodarone as we did in our case. In addition, the combination of amiodarone and mexilitine has been shown to work synergistically and has a better outcome in complex ventricular arrhythmia management.¹¹

Another challenge is that amiodarone being lipophilic has a prolonged elimination half-life and remains in the body for a long time even after its discontinuation. However, additional add-on drug therapy certainly will decrease the serum level of amiodarone and thereby mitigating toxic dose-related side effects. This logical basis of management in our patient turned out to be quite successful; however, generalisation of this concept in treatment of all may remain clinically questionable. One argument for such an assumption could be that a small subgroup of patients may possibly experience clinical worsening because of the inherent neurotoxic side effects of other antiarrhythmic drugs such as mexilitine.

Learning points

- ▶ Amiodarone is the cornerstone of medical management for a wide variety of cardiac arrhythmias.
- ▶ Neurological side effects of amiodarone are usually underappreciated in routine clinical practice and rarely become a part of the differential diagnosis of neurological clinical presentations.
- ▶ When culpability of amiodarone induced neurological effects is suspected, discontinuation of amiodarone could be challenging.
- ▶ Catheter ablation or alternative antiarrhythmic medications such as mexilitine are a plausible solution.

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