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CASE REPORT

Musical hallucinations induced by drugs

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ABSTRACT

Dipyridamole is an antiplatelet agent and a vasodilator which is increasingly being used for the secondary prevention of ischaemic stroke and transient ischemic attack, either alone or in combination with acetylsalicylic acid. We describe an 83-year-old woman who had developed musical hallucinations within days of initiating dipyridamole. Her psychiatric and neurological evaluation was otherwise unremarkable. After the discontinuation of dipyridamole the hallucinations ceased within a couple of days. To the best of our knowledge this is the first case of auditory hallucinations associated with dipyridamole reported in the literature.

Key words: dipyridamole, musical hallucinations, adverse drug reaction

Case history

J was an 83-year-old widow, who had lived on her own since the death of her husband nine years previously. She was independent in her day-to-day living, enjoyed reading and gardening. She used spectacles and was awaiting cataract surgery, and for the past twenty years had used a hearing aid in her right ear. Informed consent was obtained from the patient for the publication of this case report.

She was referred to our old age psychiatric service by her general practitioner for "hearing music in her head." Three months before she had presented to the emergency department with transient weakness in her left arm. Computerized tomography (CT) of the brain at the time was unremarkable, and she was reviewed by a neurologist the following week and a diagnosis of transient ischemic attack was made. She was started on dipyridamole 150 mg twice daily and soon began to report hearing music in her head. The music consisted of songs she used to sing in a church choir and when accompanying her mother on the piano as a child. Although this experience was pleasant to begin with, she soon found it annoying. The music was constant and she had no control over it, leading to

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mild insomnia. She realized that the experience occurred only within her own head.

J had experienced a similar episode of musical hallucinations nine years ago. At that time she had been taking dothiepin for a period of three months for the treatment of insomnia following her husband's death. The musical hallucinations had stopped when she discontinued taking dothiepin. She otherwise had no prior psychiatric history. She had never reported hearing voices or experiencing hallucinations in any other modality.

Her medical history included controlled hypertension and bilateral sensorineural deafness. Her daily medications were metoprolol controlled release 47.5 mg, cilazapril 5 mg, aspirin 150 mg, folic acid 5 mg, omeprazole 20 mg and the recently initiated dipyridamole 150 mg twice daily. She had no significant family medical/psychiatric history or substance use history.

On mental status examination, she was wearing a hearing aid in her right ear which had not been functioning well. There was no evidence of psychotic symptoms or neurovegetative symptoms of depression. She scored 30 out of 30 on the standardized Mini-mental State Examination (MMSE). She scored 1 out of 15 on the 15-item Geriatric Depression Scale making depression unlikely, and 9 on the Beck Anxiety Inventory indicating a very low anxiety level.

She was initially advised to use distraction and relaxation techniques for the musical hallucinations. She was started on risperidone 0.5 mg at night and this decreased the intensity of the musical hallucinations. This was stopped after three weeks because of daytime somnolence. She was also referred for an audiology review and was given a new set of hearing aids. However, the musical hallucinations continued.

In consultation with a neurologist, we decided to discontinue dipyridamole because the onset of the musical hallucinations coincided with the initiation of this medication. The musical hallucinations stopped a couple of days following the discontinuation

Due to the sudden onset of musical hallucinations with the initiation of dipyridamole and their spontaneous resolution following discontinuation of the same medication, we concluded that this patient's musical hallucinations were caused by dipyridamole. In order to confirm that dipyridamole was the causative agent, we suggested restarting the medication but J was unwilling to accept this challenge.

Discussion

The prevalence of musical hallucinations was reported to be 0.16% in a large sample in a general hospital setting (Fukunishi *et al.*, 1998). However, a much higher prevalence of 2.5% was reported in a sample of elderly subjects with audiological complaints (Cole *et al.*, 2002). Musical hallucinations in older people have been associated with multiple risk factors (Wang, 2005), with hearing impairments and medication side effects commonly being implicated. Other risk factors include advanced age, history of tinnitus or hyperacusis, female gender, psychiatric conditions (e.g. obsessive compulsive disorder,

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major depressive disorder, bipolar disorder, anxiety disorders), cognitive disorders (e.g. delirium and dementia) and neurological conditions (e.g. tumors, seizure disorders, stroke, cerebral aneurysm, central nervous system infections and brain lesions in the dorsal pons, temporal lobes and frontal lobes).

The phenomena of musical hallucinations may take the form of songs, musical instruments, or even birds singing. The content of the hallucinations is usually familiar to the person, with patients commonly reporting hearing childhood, religious or operatic tunes. In most instances, the hallucinations are melodious, although they may be non-melodious, or they may become fragmented over time (Berrios, 1990).

The etiology of musical hallucinations is unclear and heterogeneous mechanisms seem to be involved (Evers and Ellger, 2004). Musical hallucinations can be interpreted as a deafferentiation phenomenon. It has been suggested that they can be compared with visual hallucinations caused by focal lesions in the occipital lobe, which lead to visual deafferentiation as in Charles-Bonnet Syndrome.

In this case the phenomena of musical hallucinations occurred on two separate occasions with dothiepin and dipyridamole in an elderly woman with hearing impairment. Tricyclic antidepressants have been implicated in musical hallucinations. It has been hypothesized that the anticholinergic effects of these medications can precipitate a chronic delirium in which there is a predisposition to perceptual disturbances, including musical hallucinations (Wang, 2005). Other drugs and substances described to induce musical hallucinations include salicylates, benzodiazepines, triazolam, pentoxifylline, propranolol, amphetamine, quinine, phenothiazines, carbamazepine, marijuana, paracetamol, phenytoin, procaine, alcohol, and general anaesthesia (Fernandez *et al.*, 1998; Gordon, 1998).

Dipyridamole inhibits the uptake of adenosine into erythrocytes, platelets and endothelial cells. This results in an increased concentration of adenosine locally and stimulates platelet adenylate cyclase which increases platelet cAMP levels. Thus, platelet aggregation in response to various stimuli is inhibited. In addition, adenosine has a vasodilator effect and this is one of the mechanisms by which dipyridamole produces vasodilation. The side effect profile of dipyridamole is generally mild and transient including vomiting, diarrhea, dizziness, nausea, headache and myalgia.

Gordon (1998) suggested that hearing impairment can predispose a person to drug-induced musical hallucinations. Non-specific mechanisms (e.g. arterial hypotension) may be implicated. In his opinion, antihypertensive drugs are particularly likely to cause musical hallucinations. Our patient was taking two antihypertensive medications (metoprolol and cilazapril) at the time of initiating dipyridamole. Dipyridamole has been reported to increase the effect of hypotensive drugs which reduce blood pressure (Medsafe website). It may also cause hypotension through its vasodilating properties. Hence, the pathophysiological mechanism of dypyridamole-induced musical hallucinations could be through arterial hypotension as suggested for drug-induced musical hallucinations by Gordon (1998). We believe that a review of medications

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that can cause hypotension is an important step in the assessment of musical hallucinations in older people with hearing impairment.

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