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Methysergide-Induced Valvular Heart Disease: A Report of 2 Cases

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ABSTRACT

Methysergide is a serotonin antagonist and is used as a long-term prophylactic treatment for migraine. Although many patients experience adequate control of migraine episodes, methysergide has been reported to cause retroperitoneal and pleuropulmonary fibrosis. Cardiovascular side effects mainly in the form of valvular fibrosis have been less recognized. We report 2 cases of methysergide-related mitral valve fibrosis.

CASE REPORTS

We present 2 cases of isolated methysergide-induced mitral valve disease.

Case 1

A 47-year-old woman presented with a heart murmur as an incidental finding prior to her planned hysterectomy. She denied any chest pain or palpitation and reported only some shortness of breath on exertion. Her medical history included migraine, episodic vertigo, trigeminal neuralgia, and a hemicolectomy for caecal volvulus. She had no history of rheumatic or ischemic heart disease, but did have a positive family history for myocardial infarction.

On examination, blood pressure was 140/80 mmHg with a sinus rhythm of 110 beats per minute. She had a loud apical pansystolic murmur radiating to the axilla with an audible third heart sound. Full blood count and urine analysis were within normal limits. Drug-induced valvular disease was suspected as the patient was previously on long-term methysergide (ergot alkaloids) for the treatment of her migraine. Her medication list included carbamazepine, clonazepam, prochlorperazine, and methysergide, which was taken continuously for 2 years. This was discontinued when her heart murmur was discovered.

Echocardiography showed severe mitral and tricuspid incompetence, mild aortic incompetence with normal left heart dimensions and systolic function. This suggested a recent onset of the condition. Despite her family history, the patient's coronary angiogram was normal. The patient underwent a mechanical mitral valve replacement, and tricuspid valve repair 6 months after methysergide was discontinued.

Case 2

A 56-year-old woman presented with worsening dyspnea on exertion. Intermittent angina with pitting edema was also noted. Her past medical history included hypertension, migraine, and coronary artery bypass surgery.

On examination, blood pressure was 130/70 mmHg with a sinus rhythm of 70 beats per minute. She had a loud apical pansystolic murmur radiating to the axilla and left sternal edge. Full blood count and urine analysis were within normal limits. Her medication included amitriptyline, ramipril, aspirin, and methysergide. The patient had been on methysergide for 8 months for migraine. This was ceased as methysergide-induced valve disease was suspected.

Echocardiography showed severe mitral valve incompetence but normal left heart dimensions. A coronary angiogram showed recurrent coronary artery disease. The patient underwent re-do coronary bypass surgery as well as a mechanical mitral valve replacement 2 months after methysergide was discontinued.

Similarities of the Cases

Histopathological findings were similar for both cases. The mitral valve was thickened (Figure 1) and expanded by a plaque-like proliferation of myofibroblastic tissue in the subendothelial region. Both anterior and posterior leaflets were involved, as were the chordae in both cases. The tissue was relatively avascular and encased the leaflet and chordal structures and had preservation of the underlying valve architecture (Figure 2). Elastin stains showed that the underlying valve architecture was maintained. Immunostaining showed that proliferative cells were positive for smooth-muscle actin, indicating that they were myofibroblasts consistent with those described in methysergide-induced valvular disease.

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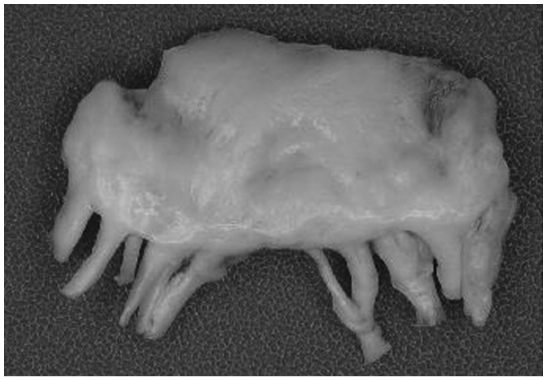

Figure 1. Macroscopic view of mitral valve showing thickened and fibrotic leaflet with fused chordae.

DISCUSSION

Several pharmacological agents cause valvular heart disease, including ergot derivatives such as methysergide and ergotamine [Bana 1974; Redfield 1992]. Methysergide is a pharmacological antagonist of serotonin (although it also has some agonist effects) and is used mainly as prophylaxis against migraine. Unwanted side effects on normal therapeutic doses occur in 10% to 15% of cases, and retroperitoneal fibrosis is likely to occur in 1% of all cases treated continuously for more than one year [Misch 1974]. Retroperitoneal and pleuropulmonary fibrosis are well documented side effects and they were first reported by Graham [1964].

Cardiovascular side effects, on the other hand, are less well recognized. These cardiovascular effects usually occur due to development of inflammatory fibrosis, which can affect the heart valves and cause valvular dysfunction. Methysergide-related valvular fibrosis can affect both left and right sides although a left-sided predominance has been suggested. This may differentiate it from the extremely similar valvular lesions related to carcinoid syndrome (associated with high serotonin levels), which mainly affects the right side of the heart. In both diseases, the fibrous plaque tends to cover but not invade the valve leaflet and chordal architecture [Mason 1977]. The changes are different from those described in rheumatic valvulopathy, where the valve structure is disrupted with presence of prominent neovascularization. The findings in both our cases were identical to those seen in ergot alkaloid–related valve disease as described by Pritchett et al [2002].

Figure 2. Elastin stain of mitral valve chordae showing maintenance of normal architecture and encasement with avascular fibrotic tissue (original magnification ×100).

There is no known gender preference for this entity, but as migraine is more common in women, we would expect a higher usage of methysergide in that gender group and therefore a higher incidence of related fibrosis. Some patients may develop systolic and diastolic murmurs during methysergide therapy. A suspicion of methysergide-related valvular heart disease should be raised if the patient has no history of previous murmur or rheumatic heart disease, a murmur is first recognized while on methysergide when no other likely cause can be found, and if the murmur worsens when the drug is continued and regresses or completely disappears over a few months when discontinued [Bana 1974].

The general thought is that methysergide-induced fibrosis will not occur if therapy is interrupted at least every 6 months. Interrupted drug regimens, however, are not always effective in reducing the development of fibrosis, as reported by Mason et al [1977], where a patient continued to progress with endocardial fibrosis over a year after cessation of methysergide. Similarly in our first patient, methysergide had been ceased for 6 months before she underwent surgery. The general recommendation remains to cease treatment on suspicion of methysergide-related fibrosis or valvular disease.

Our general advice to practitioners, cardiologists, and cardiac surgeons would be to maintain an adequate level of suspicion because, although methysergide-induced valvular disease is uncommon, it is a well recognized entity. Regular clinical follow-up of patients on long-term methysergide should take place every 6 to 12 months. If a new murmur is detected, methysergide should be discontinued and echocardiogram follow-up is recommended.

From the surgical point of view, multileaflet involvement is the usual picture, as in both our cases where both mitral valve leaflets were involved. Valve repair in these cases would be unsuccessful or at least very difficult. Valve replacement is therefore the usual surgical management for this type of valve pathology.

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