REVIEW ARTICLE

Neurologic Disorders Associated with Mitral Valve Prolapse

Alan C. Jackson

ABSTRACT: Mitral valve prolapse has been reported to be associated with a variety of neurologic disorders, including cerebral ischemia, transient global amnesia, migraine, autonomic dysfunction, and psychiatric disease. The evidence supporting these associations and possible pathogenetic mechanisms are discussed. Some neurologic disorders may be direct complications of mitral valve prolapse, while others may occur as part of an underlying genetic defect or common link.

RÉSUMÉ: Affections neurologiques associées au prolapsus de la valvule mitrale Une variété d'affections neurologiques telles que l'ischémie cérébrale, l'amnésie globale transitoire, la migraine, la dysfonction du système nerveux autonome et des désordres psychiatriques, ont été décrites en association avec le prolapsus valvulaire mitral. Les données qui sont en faveur d'une telle association ainsi que les mécanismes pathogéniques éventuels sont discutés. Certaines affections neurologiques peuvent être une complication directe du prolapsus valvulaire mitral, alors que d'autres sont la manifestation d'un défaut génétique sousjacent ou lui sont communément associées.

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Mitral valve prolapse (MVP) is a common cardiac abnormality, and has been the subject of numerous reports in the current medical literature. General aspects of the disorder have recently been reviewed.[1-4] Over the past decade there has been considerable interest and, in some cases, controversy regarding the association of neurologic disorders and MVP. Some associations have not yet been firmly established, and the basis for others still remains quite speculative. The evidence for these associations will be reviewed.

Diagnosis of Mitral Valve Prolapse

In MVP one or both of the mitral valve leaflets prolapse (or balloon back) into the left atrium during left ventricular systole. The diagnostic criteria for MVP depend on the methods of study used, which may include auscultation, imaging techniques, or pathologic examination. The auscultatory features are one or more nonejection clicks and a late systolic murmur. Certain maneuvers, including changes in posture, may be helpful in eliciting these signs. MVP is identified by M-mode echocardiography on the basis of abnormal posterior motion, either late systolic or pansystolic, of the mitral leaflets.[1] Limitations of M-mode echocardiography include imaging in only the anterior-posterior plane, when the prolapse may occur in a superior direction, and false-positive findings due to abnormal orientation (in an inferior direction) of the transducer.[5] Two-dimensional echocardiography has the advantage of visualizing more of the mitral leaflets, and appears to be a more sensitive technique for diagnosing MVP than M-mode echocardiography.[5] There is an important subjective component in the interpretation of echocardiograms. Angiocardiography is invasive, the anterior mitral leaflet may not be well visualized, and there is considerable doubt about the exact criteria needed for diagnosis.[1] Some patients without auscultatory findings have prolapse on angiocardiography or echocardiography (silent MVP). It is not clear whether the pathologic substrate or risk of complications is different in these patients.

The basic pathologic feature of MVP is thickening of the spongiosa, a myxomatous connective tissue, with invasion and

From the Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland
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Reprint requests to: Dr. Alan C. Jackson, Department of Neurology, Johns Hopkins University, 600 N. Wolfe St./Meyer 6-181, Baltimore, Maryland, U.S.A. 21205

disruption of the fibrosa, which is composed of dense layers of collagen and forms the basic support of the leaflet.[6] The defect in MVP may be due to "wear and tear", or there could be an altered composition of the collagen.[7,8] The leaflets become voluminous, thickened, and elongated; the chordae tendineae are usually elongated and thickened. MVP occurs in patients of all ages. The prevalence is about 6% in both clinical and pathologic studies.[6,9,10]

Cerebral and Retinal Ischemia

Barnett and co-workers first recognized the association of MVP with cerebral ischemia.[11,12] Barlow and Bosman[13] had previously reported a woman with MVP who presented with transient left arm weakness at age 23. Retinal ischemic events have also been described.[14] Barnett et al[12] initially documented the association of MVP and cerebral ischemia in a series of patients that had careful evaluation for associated cardiac lesions. Subsequently, they performed a case-control study which substantiated the association.[15] The prevalence of MVP was 40% in a group of 60 unselected patients, 45 years and younger, who had experienced cerebral and retinal ischemic events. Only six patients (10%) had other potential reasons for ischemia. The prevalence of MVP was 6.8% in an age- and sex-matched control group. Scharf et al[16] also found the prevalence of MVP was significantly higher in young patients with unexplained cerebral ischemia than in asymptomatic controls (Table 1). Egeblad and Sorensen[17] were unable to confirm this association in a European case-control study. It is not clear whether this reflects a difference in their study populations or a difference in their diagnostic criteria for MVP.

Additional studies of the prevalence of MVP in cerebral ischemia are summarized in the Table. Various selection criteria were used in these studies. In general, a high prevalence of MVP (13-35%) was found in young patients with cerebral ischemia. The prevalence was usually normal in older patients or in patients of unselected age. Because of the possibility of investigator bias, the uncontrolled studies should be considered of less consequence. Sandok and Giuliani[26] found the prevalence rate for cerebral infarction was at least four times the expected rate in patients with MVP that were referred for echocardiography.

Thromboembolism from the abnormal mitral valve is the best supported mechanism for the association of MVP and ischemic events. There is clinical, angiographic, and pathologic evidence to support this mechanism.[27] Cerebral and retinal symptoms and signs are focal, rather than diffuse. Retinal vascular occlusions have been observed in association with MVP.[28] On angiography, branch or "trunk" occlusions have been observed, with the subsequent disappearance of some of the lesions. Atheromata are not observed. Pomerance[29] has noted fissuring and thrombus formation on myxomatous mitral valves. Aggregates of platelets and fibrin may form in the angle between the posterior leaflet of the mitral valve and the left atrial wall.[30] In a patient with ischemic events, thrombus was demonstrated by two-dimensional echocardiography, and subsequently confirmed pathologically following surgery.[31] Four fatal cases have been reported with postmortem examinations.[32-35]

The risk of stroke in young patients with MVP is low, and has been estimated at 1/6,000 per year.[36] At the present time there are not any good indicators to predict which individuals with MVP are prone to stroke. Two recent studies from European centers have suggested that more extensive valve involvement, with thickening of the mitral valve, may be associated with a greater risk of cerebral ischemia.[37,38] Cerebral ischemia may also occur with MVP in older patients. However, it is more difficult to assess the importance of MVP in these patients because of the increased prevalence of atherosclerotic-thrombotic disease and other types of heart disease with increasing age. Recurrent ischemic events are not uncommon. Forty-four percent of young patients with cerebral ischemia had recurrent events at the time their MVP-associated ischemia was recognized.[39] Empirical therapy with platelet antiaggregants has been recommended.[40]

Familial Stroke

The prevalence of MVP is increased in some families, and it may be inherited as an autosomal dominant trait.[41] Rice et al[42] reported four individuals in a 27-member family with cerebral or retinal ischemia occurring at a young age. Ischemic events have also been described in a pair of monozygotic twins.[43]

Table 1: Mitral Valve Prolapse in Cerebral Ischemia

Investigators	No. of Patients	Age (yrs.)	% of Patients with MVP	% of Controls with MVP
Barnett et al[15]	60	6-45	40	6.8 ($p<.001$)
Barnett et al[15]	141	49-87	5.7	7.1 ($p>.05$)
Scharf et al[16]	47	≤45	28	8.5 ($p<.01$)
Egeblad and Sorensen[17]	30	24-39	10	0 ($p>.05$)
De Bono and Warlow[18]	117	25-80	11.1	3.8 ($p>.05$)
Bensaid et al[19]	20	28-40	20	No Controls
Bensaid et al[19]	116	40-70	5.2	No Controls
Fieschi et al[20]	14	<45	21.5	No Controls
Fieschi et al[20]	106	>45	2.9	No Controls
Kouvaras and Baroulas[21]	66	<50	34.8	No Controls
Tharakan et al[22]	38	<40	13	No Controls
Greenland et al[23]	100	Mean 70	1	No Controls
Smith and McKnight[24]	96	Unknown	5.2	No Controls
Gagliardi et al[25]	88	14-68	23.9	No Controls

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Transient Global Amnesia

Transient global amnesia is a clinical syndrome characterized by a sudden short-term memory defect and retrograde amnesia, usually lasting a few hours.[44-46] Although the etiology is uncertain, a cerebral ischemic and an epileptogenic origin are the two main proposed theories. Many investigators believe ischemia of medial temporal structures is a common cause. Shuping et al[46] described a patient with MVP and multiple recurrences of transient global amnesia. They ceased following mitral valve replacement. Jackson et al[47] evaluated the prevalence of cardiac abnormalities in 53 transient global amnesia patients, and in the same number of age- and sex-matched control subjects. MVP was significantly more common in transient global amnesia patients (24.5%) than controls (7.5%). Recurrent episodes were common in the patients with MVP (46%). MVP may produce transient global amnesia by a thromboembolic mechanism, as has been proposed in patients with MVP and cerebral ischemia.

Infective Endocarditis

MVP is a recognized cardiac lesion which predisposes to infective endocarditis. Cerebral embolism is the most common neurologic complication of bacterial endocarditis, occurring in 17% of 218 patients.[48] Cerebral ischemia has been reported in 20-50% of patients with MVP and infective endocarditis, and alpha-hemolytic streptococci are the most common causative organisms isolated.[49,50] Evidence of infective endocarditis should be sought in all patients with MVP and ischemic events.

Migraine

Litman and Friedman[51] reported migraine in 28% of 230 patients with MVP. Subsequently, Amat et al[52] reported MVP in 20% of vascular headache patients. Gamberini et al[53] found MVP in 20% of common migraine patients, and migraine in 51% of patients with MVP. These three studies all lacked control groups. In a case-control study, Spence et al[54] found MVP in 25% of patients with classic migraine and in 11% of control subjects. These studies support an association of MVP and migraine, but confirmation will require additional properly constructed studies. Platelet abnormalities have been described in migraine[55,56] and MVP (see below), and both may have associated cerebral ischemia.

Intracranial Aneurysms

Jackson[57] reported five patients with MVP and intracranial aneurysms, including three also with cerebral ischemic events. It is possible that the association in these case reports was by chance alone, and further study is needed to confirm the association. Mesodermal disturbances involving collagen and elastic tissue in the vasculature could provide a basis for both disorders. Abnormal collagen has been observed in both MVP and ruptured cerebral aneurysms.[8,58] MVP has also been reported to be associated with von Willebrand syndromes and sickle cell disease, suggesting a linked connective tissue defect.[59-61] Hence, there may be a common ground for certain cerebrovascular, cardiac, and hematologic disorders.[62]

Seizures

There have been occasional reports of patients with seizures and MVP.[63-65] The association would be most understandable if the seizure disorder was related in some way to cerebral ischemia. At the present time, there is little evidence to support an important association.

Muscular Dystrophies

Winters et al[66] reported the association of MVP and myotonic dystrophy in a single large kindred. Twenty-five relatives were screened, and they found 8 with both, 2 with myotonic dystrophy alone, and 1 with MVP alone. Two reports have described patients with the combination of myotonic dystrophy, MVP, and cerebral ischemia.[33,67] MVP has also been reported in Duchenne muscular dystrophy.[68-70] Sanyal et al[70] speculate that MVP is an expression of the underlying cardiomyopathy characteristic of Duchenne muscular dystrophy, rather than due to isolated dystrophic involvement of the mitral valve leaflets.

Platelet Activity

A number of studies have provided evidence of platelet hyperreactivity in a significant number of MVP patients.[16,71-74] Platelet coagulant hyperactivity, increased platelet factor 4, increased ß-thromboglobulin, and shortened platelet survival times have been demonstrated. However, Scharf et al[16] did not find any significant difference between the elevated plasma ß-thromboglobulin levels in young patients with cerebral ischemia with or without MVP. Platelet activation has been shown in asymptomatic MVP patients, as well as in MVP patients with thromboembolic events. The altered platelet activity may be a consequence of interaction of platelets with the abnormal myxomatous mitral valve. It has been speculated, but is unproven, that MVP patients with platelet hyper-reactivity may have an increased risk of thromboembolism.

Autonomic Dysfunction

Wooley[75] has suggested that the autonomic dysfunction in MVP patients has been unrecognized for at least 120 years, and has masqueraded under such diagnoses as DaCosta's syndrome, soldiers heart, effort syndrome, and neurocirculatory asthenia. A number of specialized investigations have been performed on MVP patients (albeit often highly symptomatic) and controls in order to assess regulation of cardiovascular function. In some patients there is evidence of a hyperdynamic state, based on changes in various hemodynamic parameters and catecholamine levels in response to postural stress or isoproterenol infusion.[76-81] Studies by Gaffney et al[80] have shown that some MVP patients have vasoconstriction, tachycardia, elevated mean blood pressure on standing, and elevated plasma norepinephrine levels. The vasoconstriction may lead chronically to hypovolemia, and the volume of blood contained in the ballooning leaflets may reduce the ventricular and stroke volume. Although a large myxomatous valve could have a facilitative role, the autonomic disturbance could be the fundamental defect causing the hemodynamic abnormalities. Chesler et al[82] feel the MVP patients studied have not been representative of patients with MVP in the general population. It is not clear how frequently autonomic dysfunction occurs in association with MVP, but it is well documented in some symptomatic MVP patients.

Psychiatric Disorders

Chronic anxiety neurosis, panic disorder, and agoraphobia are psychiatric disorders reported to be associated with MVP.

Crowe[83] and Klein and Gorman[84] have recently reviewed the association of MVP and panic disorder. A number of studies have shown an increased prevalence of MVP (15-50%) in patients with panic attacks or agoraphobia. However, Hickey et al[85] were unable to confirm an association of MVP and agoraphobia. It has been speculated that MVP may actually cause panic attacks. Susceptible anxious individuals may respond to MVP symptoms with fear and sympathetic arousal, leading to a further increase in their symptoms and a vicious circle.[86] MVP has also been reported in patients with primary disorders of sleep, including narcolepsy.[87]

Sudden Death

Patients with cardiac symptoms of MVP, such as dizziness or syncope, may present for neurologic evaluation. Although sudden death is a cardiac, rather than neurologic, complication of MVP, it is discussed here because warning symptoms may occasionally be recognized. Sudden death is rare in MVP. In many cases the clinical details are scanty or absent, and in some cases factors other than MVP could be incriminated.[88] A variety of arrhythmias are associated with MVP.[89] It is likely that cardiac arrhythmias, especially ventricular fibrillation, are the cause of sudden, unexplained death. Chesler et al[30] have found thrombotic lesions in the angle between the posterior leaflet and the left atrial wall containing aggregates of platelets and fibrin in some fatal cases. It is possible that arrhythmias could be caused by coronary thromboembolism.

The present problem is in identifying patients at risk of sudden death. Patients with ventricular ectopy or a convincing history of palpitations, presyncope, and syncope should be subjected to 24-hour ambulatory monitoring. Patients exhibiting dangerous arrhythmias should be maintained on antiarrhythmic drugs with regular monitoring.[90] Dizziness and syncope in MVP patients are usually attributed to cardiac arrhythmias, but orthostatic hypotension is another possible cause.[91]

Conclusions

Patients with MVP are frequently seen in the practice of neurology. Some neurologic disorders have recognized associations with MVP. A neurologic disorder may be a direct complication of MVP, or the basis for the association may be an underlying genetic defect or common link. Evaluation of potential associations requires appropriate controls, since there is a substantial subjective element in the interpretation of echocardiograms which may introduce considerable bias. Pathologic studies should help to confirm specific associations in the future, and they may provide evidence supporting particular pathogenetic mechanisms. Markers for specific complications, neurologic or other, have not yet been well identified. In addition to clinical studies, identification of the fundamental defect in MVP, perhaps at the molecular level, may help to unravel the enigma surrounding this disorder.

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