# Acute Myocardial Infarction and Friedreich's Ataxia

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## Abstract

*While cardiac disease is noted in 90% of patients with Friedreich's ataxia (FRDA), the finding of coronary artery disesase is unusual. To the best of our knowledge only two cases of acute myocardial infarction (AMI) has been reported in patients with FRDA. Large vessel CAD has not been reported previously in patients with FRDA. We report a young patient with AMI and obstruction of large epicardial arteries.*

## Introduction

Friedreich's ataxia (FRDA) is an autosomal recessive neuromuscular disorder characterized by spinocerebeller ataxia, loss of tendon reflexes and skeletal deformities. Its association with heart disease has been known since Friedreich's first description in 1863 and is now believed to be present in 90% of patients.[1-3] The most common cardiac pathology is left ventricular hypertrophy.

Coronary artery disease (CAD) is distinctly unusual with autopsy studies demonstrating only small vessel abnormalities. The functional significance of these have been challenged.[3] To the best of our knowledge only two cases of acute myocardial infarction (AMI) have been reported in patients with FRDA,[4,5] though few reports have alluded to suspected cases.[2,5,6] Large vessel CAD has not been reported previously in patients with FRDA. We report a young patient with AMI and obstruction of large epicardial arteries.

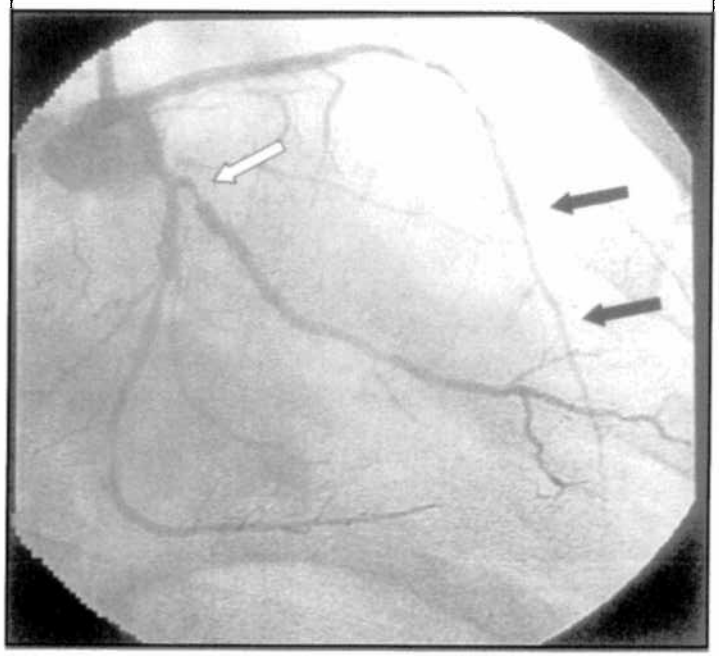
## Case Report

A 35-year-old Caucasian male with FRDA presented for evaluation of chest pain. In childhood he was noted to be slow and clumsy in motor activities such as running and throwing. At age nine, he had bilateral pes cavus corrected surgically. As a teenager, he fell frequently and had difficulty ambulating. He has been wheelchair-bound since age 20. Over the past year, increased upper extremity weakness and incoordination has been noted. Genetic testing had confirmed him to be homozygous for FRDA.

Over the last two years, he experienced intermittent, retrosternal chest pain which was exacerbated markedly eight months prior to evaluation. He then presented to the emergency room with abrupt onset of severe, crushing retrosternal chest pain with radiation to left arm. This was associated with acute onset of dyspnea and diaphoresis. He did not have diabetes mellitus or hypertension and denied use of alcohol or smoking. Family history for premature coronary artery disease was negative. The most recent lipid profile was as follows: total cholesterol 156 mg/dl, triglyceride 238 mg/dl, HDL 26 mg/dl, and LDL 82 mg/dl. Homocysteine level was 19 μmol/L.

On physical examination, the patient was noted to be a well-developed, dysarthric caucasian male in no acute distress. Vital signs revealed blood pressure of 120/60, heart rate of 100, respiratory rate 18 and he was afebrile. Cardiovascular examination revealed normal heart sounds, a non-displaced PMI and no murmurs

Figure 1.— The right anterior oblique view of the left coronary artery angiogram showing a diffusely narrowed left anterior descending artery (black arrows) without focal abnormality and a small diagonal branch with a 60% proximal lesion. Circumflex artery had a 60% segmental occlusion and a large obtuse marginal branch (culprit vessel) with 90% proximal stenosis (white arrow).



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or features of heart failure. Musculoskeletal examination was significant for pes cavus, hammer toes, and feet inversion. He was areflexic and had loss of proprioception and vibration sensation in lower extremities. He had dysmetria with poor coordination bilaterally and Grade 2/5 lower extremity muscle strength with bilateral extensor plantar response.

EKG changes were consistent with acute infero-lateral MI and the cardiac injury markers confirmed this. His peak troponin I was 46 ng/ml (n<2.0). Echocardiogram done urgently showed apical and inferior hypokinesis and left ventricular hypertrophy (LVH) with wall thickness of 1.8 cm. Cardiac catheterization revealed a diffusely narrowed left anterior descending artery (LAD) without focal abnormality. The diagonal branch was small with a 60% proximal lesion. Circumflex artery had a 60% segmental stenosis and the large obtuse marginal branch with 90% proximal stenosis was believed to be the culprit vessel. A 40% stenosis of the distal right coronary artery was noted. Left ventriculogram showed severe hypokinesis of left ventricular apex and an ejection fraction of 40%. Percutaneous transluminal coronary angioplasty with stent placement of the obtuse marginal vessel was done successfully with TIMI grade III flow. Patient was placed on clopidogrel, aspirin, and metoprolol.

A month later, he was re-admitted for an acute non-Q wave MI with a peak troponin I of 47 ng/ml. Subsequent cardiac catheterization revealed acute occlusion of the stented vessel and the ejection fraction was 35%. Coronary artery bypass was then performed successfully using saphenous vein grafts to the two obtuse marginal branches sequentially, and to the diagonal branch of LAD. During the subsequent month, he developed recurrent chest pain with several hospitalizations necessitating a cardiac catheterization, which revealed complete occlusion of the obtuse marginal graft and 60% occlusion of the graft to the diagonal branch of LAD.

Stress thallium scan showed a large non-reversible perfusion defect involving the lateral, inferior wall and apex of the left ventricle. He was managed conservatively with aspirin, warfarin, metoprolol, quinapril, atorvastatin, folic acid and multivitamins.

## Discussion

Cardiac involvement is noted in 90% [1-3] of patients with FRDA and has been studied extensively using EKG,[7,8] cardiac catheterization,[9] echocardiography,[10-12] radionuclide studies,[13] and autopsy series.[2,3,5,14]

The main feature of heart disease associated with FRDA is concentric LVH,[10-12] but asymmetrical septal hypertrophy and left ventricular outflow tract obstruction[9] may also occur. In some cases, cardiac features precede neurological manifestation.[15-17] Symptoms such as chest pain, palpitations and dizziness occur in the minority of patients. However, in Hewer's series 12% had angina and 73% had cardiac symptoms before death.[5] They often have arrhythmias, syncope and sudden death. For these reasons, coronary disease has been suspected for many years. However, most reviews and reports on this subject dismiss the coronary lesion as not functionally significant, largely on the basis of Hewer's interpretation.[3] He found that only 9% of the 900 arteries had a reduction in the luminal diameter by 50% and concluded that it was not responsible for the extensive muscle fibrosis that was observed. Rather, he believed these coronary lesions to be a secondary phenomena. The narrowing of coronary arteries is, however, not described in other muscular dystrophy with myocardial involvement and has not been observed in myocardial fibrosis of other etiology.[2] Though he reports on 27 cases, histological specimens were available in only 16 cases. Only three complete hearts were available to him and 100 sections each of 30um could not have examined the entire 100mm coronary artery. It is possible that the incomplete histopathologic study of the coronary arteries described in these studies may have obscured this finding from the investigator.

James et al. demonstrated small coronary artery occlusions caused by focal fibromuscular dysplasia, intimal proliferation, medial degeneration and fibrosis.[18] Positive acid-Schiff deposits are noted in the subintima and resemble amyloid. However, specific staining for amyloid, fat and fibrin has been consistently negative. Involvement of large coronary artery has been noted in few cases.[18-20] Nadas et al. went on to suggest that CAD might be responsible for myocardial damage in FRDA. A thallium stress imaging reported by Casazza et al. demonstrated perfusion defects in three of the thirteen asymptomatic FRDA patients with LVH.[21] Angiographic studies were limited by the use of non-selective coronary catheterization. Since the inception of selective coronary artery angiography in 1958,[22] no explicit reference has been made to coronary vessels in FRDA patients.

In Hewer's study of 82 fatal cases of FRDA, four patients were clinically diagnosed with MI, of these one had a confirmed diagnosis at autopsy. Calvo et al. reported a case of AMI involving microvascular disease and spasm of coronary arteries.[4] No other confirmed cases of MI in FRDA have since been reported. Our patient had an acute myocardial infarction and left ventricular hypertrophy. On coronary angiography the culprit lesion was determined to be a proximal stenosis of a large epicardial vessel. In view of the above deliberations we believe that the finding of acute myocardial infarction and large vessel coronary artery disease in our patient raises the possibility of cause and effect, however his lipid abnormality and hyperhomocysteinemia could be alternate explanations.

The pathogenetic mechanisms leading to myocardial infarction in our patient may be multifactorial. Multiple case reports [3,5,6,15,23] make reference to thrombus formation in the heart chambers. In Hewer's autopsy series, twelve out of twenty seven patients showed thrombus formation, of which four cases presented with thrombosis in the heart and in a major artery including the left middle cerebral and the superior mesenteric artery.[5] Our patient showed thrombosis of stent and later occlusion of the grafts. Thrombosis may have been the primary cause of the cardiac lesion in this patient, and certainly played a significant role once the endothelium was disrupted by these procedures. Vasospasm was reported as one of the mechanisms causing angina.[7] However, the role of this process in our patient is difficult to determine. His lipid abnormality and hyperhomocysteinemia could be added explanations as noted in the general population at large. There are no reports of homocysteine abnormalities in patients with FRDA. Diabetes mellitus is noted in 10-23% of the FRDA patient,[1,5] but was not present in our case.

Left ventricular hypertrophy is prevalent in FRDA patient and may have a direct or an indirect impact on mortality. LVH is independently associated with increased incidence of cardiovascular disease and cardiovascular mortality.[24] Diminished coronary vasodilator reserve, increased myocardial oxygen demand, subendocardial ischemia, lethal arrhythmias, and diminished ventricular

performance may explain the increased risk associated with left ventricular hypertrophy.[25] In a meta-analysis of 39 randomized double blind clinical trials performed through June 1995, the use of angiotensin-converting enzyme inhibitors, calcium-channel blockers, diuretics, or b-blockers was associated with respective reductions in left ventricular mass of 13%, 9%, 7%, and 6%.[26] This prominent effect of ACE inhibitors on left ventricular hypertrophy regression may reflect their action on local renin-angiotensin system in addition to the effective blood pressure control. This theory is further supported by the evidence that angiotensin II exerts direct trophic effect on myocardial cells [27]. Although the use of these agents and their impact in FRDA patients is not specifically reported, it is likely to be beneficial.

Recent advances have improved the understanding of FRDA at a molecular and genetic level. Chamberlain et al. localized the gene for FRDA to chromosome 9 q13 in 1988.[28] In 1996, Campuzano et al. discovered the FRDA gene, which is an intronic GAA triplet repeat expansion.[29] This led to an accurate genetic testing for this disease. Researchers showed that frataxin, the protein encoded by FRDA gene, [30] is an iron transporter protein in mitochondria.[31] Babock et al. found that the shortage of this protein in yeast cells led to a toxic build up of iron in the mitochondria. When excess iron reacted with oxygen, free radicals were produced leading to cell destruction.[31] This syndrome of ataxia and neuropathy, in association with diabetes, cardiomyopathy, deafness and optic atrophy, has all the hallmarks of a mitochondrial disease. Hence, FRDA may very well turn out to be the commonest mitochondrial disease.[1] Further investigation in this area may result in the development of an effective treatment for this condition.

Currently, there is no cure for FRDA, and cardiac disease remains the primary cause of death.[5,7,15] Median survival is 35 years.[5] Our patient, 35 years of age, presented with AMI involving large epicardial vessels. To our knowledge, this has been demonstrated for the first time angiographically in a patient with FRDA. Improved awareness and early intervention may significantly affect the outcome. With recent advances in diagnosis and possibly treatment of FRDA, we anticipate a larger number of patients to live longer. The impact of premature coronary artery disease may become more relevant; thus, it may be appropriate to evaluate for coronary artery disease in these patients. In addition, the role of left ventricular hypertrophy and thrombosis in these patients needs to be studied further.


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