CASE STUDY

Raised factor VIII is associated with coronary thrombotic events

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Abstract

Coagulation is triggered during the onset of myocardial infarction, resulting in vascular occlusion. However, a causal role for individual haemostatic factors in the development of thrombotic occlusion is not established. Three cases (all relatively young women) are reported of raised factor VIII associated with myocardial infarction. Two patients presented acutely with myocardial infarction at a relatively young age with no preceding history of angina. The other patient had had venous thrombosis when young and activated protein C resistance (APCR), without the presence of factor V Leiden. A functional relation exists between APCR and factor VIII; therefore, raised factor VIII may contribute to APCR and the increased thrombotic risk in patients without factor V Leiden. Factor VIII is an important risk factor for atherothrombotic events, including sudden death, in patients with vascular disease. These cases support the association of raised factor VIII with acute thrombotic events, even in patients without significant underlying atheromatous disease.

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Keywords: factor VIII; thrombosis; myocardial infarction; activated protein C resistance

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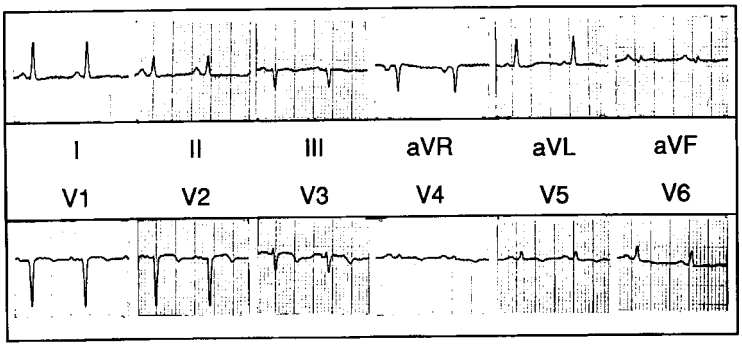

Figure 1 ECG from case 1 showing severely reduced R wave amplitude and T wave inversion in the precordial leads, consistent with previous anterior myocardial infarction.

Case 1

A 50 year old Asian woman was referred having had an extensive anterior myocardial infarction four months previously in India. She was asymptomatic at presentation and had been prescribed aspirin 75 mg and slow release isosorbide mononitrate 60 mg. She had a history of hypertension, and a tuberculous cervical lymph node had been excised 14 years previously. She was a non-smoker with a family history of diabetes, renal disease, and coronary artery disease. There was no history of previous thrombotic events and no other cardiovascular risk factors.

Examination showed her to be obese (body mass index 35 kg/m^2), with a pulse of 80 beats/min, and blood pressure 130/70 mm Hg. There were no abnormal clinical findings.

Investigations showed normal full blood count, urea, creatinine, and electrolytes, a raised serum cholesterol of 6.0 mmol/l, and triglyceride of 1.09 mmol/l. An ECG revealed changes consistent with an extensive anterior myocardial infarction (fig 1). Coronary angiography showed normal unobstructed coronary arteries. Left ventriculography showed extensive anterior hypokinesia with an apical aneurysm. Further tests for thrombophilia showed raised plasma factor VIII (3.32 iu/ml; normal range 0.45–1.58), protein C (1.63 iu/ml; normal range < 1.4), and fibrinogen (4.12 iu/ml; normal range 1.8–3.6). Thrombin time was shortened to 13 seconds (normal range 15–19), but clotting was otherwise normal. Antithrombin III, protein S, protein C, erythrocyte sedimentation rate, and C reactive protein were all normal; autoantibodies were negative.

Sixteen months after her myocardial infarction, her factor VIII level was still raised at 2.00 iu/ml. In view of this and the left ventricular aneurysm she has been prescribed oral anticoagulation with warfarin.

Case 2

A 32 year old white woman was referred for investigation. At the age of 27 she had had an anterior myocardial infarction, which resulted in left ventricular aneurysm and impaired left ventricular function. Subsequently she had

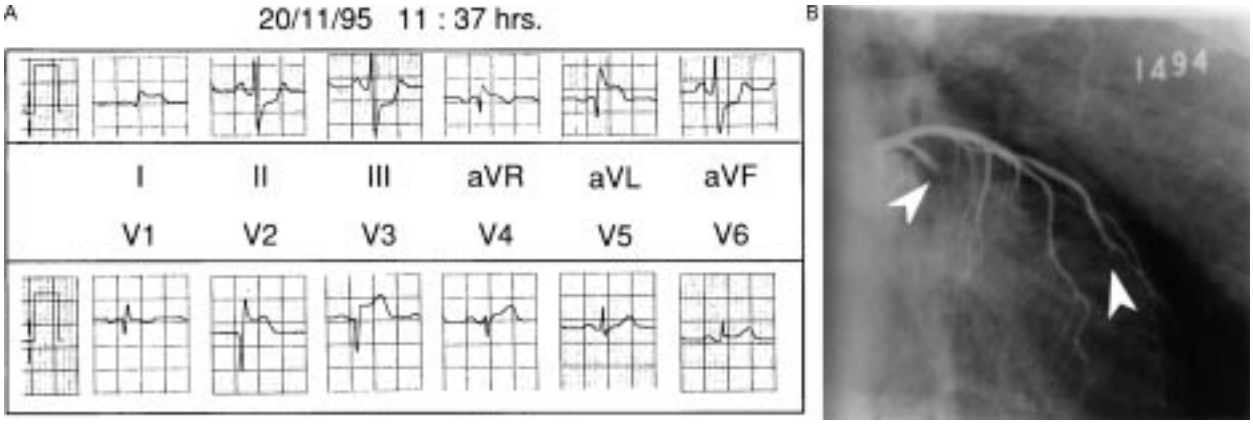

Figure 2 (A) ECG from case 3 recorded two hours after the onset of chest pain showing elevation in the anteroseptal and anterolateral leads, ST segment depression in the inferior leads, and Q waves. (B) Angiogram showing proximal occlusion of the circumflex artery (arrowed) and proximal occlusion of a branch of the diagonal branch of the left anterior descending coronary artery (arrowed).

experienced exertional angina during pregnancies, and since then only on heavy lifting. Her history was notable for gestational diabetes and acute pancreatitis secondary to gallstones, requiring a cholecystectomy in 1993. She has three children and her first two pregnancies required emergency caesarean sections because of fetal distress. She was a non-smoker with a strong family history of ischaemic heart disease affecting her grandparents and great grandparents; her father had developed angina at the age of 34. There were no other cardiac risk factors and clinical examination was unremarkable.

ECG was consistent with previous anteroseptal infarction, with persistent 1 mm ST elevation in V2 and T wave inversion in the inferolateral leads. Cardiac catheterisation showed 90% stenosis of the proximal left anterior descending coronary artery with TIMI grade I-II flow. Left ventriculography showed an apical aneurysm with good overall left ventricular function. Full blood count, urea, and electrolytes were normal. Thrombin time was reduced to 12 seconds but clotting was otherwise normal. Further tests for thrombophilia showed raised plasma factor VIII (3.03 iu/ml) but normal concentrations of antithrombin III, fibrinogen, lupus anticoagulant, and proteins C and S.

Case 3

A 58 year old white woman was admitted with an acute anterolateral myocardial infarction. She had no preceding history of angina but had hypercholesterolaemia, smoked 15 cigarettes a day for 40 years, and had a strong history of thromboembolic disease. In 1964 she had a left deep venous thrombosis while taking the oral contraceptive pill, which she subsequently discontinued. In the early 1970s she had a left femoral vein thrombosis, followed by thrombophlebitis in the inguinal area in 1976 and 1990. Her daughter had also had a deep venous thrombosis during pregnancy and her father had died of a myocardial infarction at age 64.

Investigations for thrombophilia two years previously had revealed a shortened activated partial thromboplastin time of 28 seconds (normal range 30–46), thrombin time reduced to 14 seconds, and normal prothrombin time. Notably she had a raised factor VIII of 1.85 iu/ml, raised prothrombin fragment 1 + 2 of 1.8 nmol/l (normal range 0.24–1.44), and activated protein C resistance (ratio 2.04 iu/ml (normal range 2.35–3.63)). Fibrinogen, protein S, protein C, and antithrombin III were all normal, and she did not have the factor V Leiden mutation.

Full blood count, urea, electrolytes, and chest *x* ray were normal on admission. Cholesterol was raised at 5.7 mmol/l and triglycerides 2.17 mmol/l. An ECG recorded two hours after the onset of chest pain (fig 2A) showed extensive acute anterolateral myocardial infarction with deep Q waves.

Chest pain and persistent ST segment elevation continued despite 300 mg aspirin, 1.5 MU intravenous streptokinase, and intravenous infusion of glyceryl trinitrate. Emergency coronary angiography revealed proximal occlusion of the left circumflex coronary artery and occlusion of a distal branch of the first diagonal artery, consistent with extensive acute coronary thrombosis (fig 2B). Angioplasty of the proximal circumflex artery achieved patency but with poor distal run off. The patient was fully heparinised.

Cardiac enzymes became severely raised with a peak creatine kinase of 8736 iu/l 12 hours after the onset of symptoms and peak lactate dehydrogenase of 4050 iu/l on the day of admission. The subsequent clinical course was complicated by supraventricular tachycardia, sepsis, renal failure, severe haemoptysis, pulmonary oedema, and cardiogenic shock. Despite inotropic support and ventilation, on day 13 she had a cardiac arrest from which she could not be resuscitated.

Postmortem examination of the coronary arteries showed smooth surfaced fibrous and fibrofatty plaques within the proximal segments of the circumflex and left anterior descending coronary arteries. No plaque fissuring, ulceration or occlusive thrombus was seen. Microthrombi were present in the distal, intramyocardial portions of the circumflex and left anterior descending arteries. The histological findings were consistent with extensive, transmural acute thrombotic infarction of the lateral and anterior left ventricular wall.

Discussion

There is abundant evidence that thrombosis is involved in the acute presentation of coronary, cerebrovascular, and peripheral vascular diseases. During the onset of myocardial infarction, coagulation is triggered culminating in vascular occlusion. Evidence supporting a role for haemostatic factors in the development of atherosclerotic lesions is more tenuous. A number of studies have examined the association of cardiovascular disease with coagulation factors (fibrinogen, factor VII, factor VIII, platelet aggregability) and fibrinolytic factors (tissue plasminogen activator, plasminogen activator inhibitor-1, Lp(a) lipoprotein, plasminogen activity). Of these, only for fibrinogen was there a strong, significant association.[1] Relatively less is known about the relation between factor VIII and cardiovascular disease risk. The PLAT study (progretto Lombardo atero-trombosi) of patients with established cardiovascular disease yielded the most convincing evidence for factor VIII as a cardiovascular risk factor.[2] It revealed that factor VIII concentration was an independent univariate predictor of vascular disease events (myocardial infarction, sudden death, cardiac death, stroke, transient ischaemic attack, and acute peripheral occlusion or ischaemia) in patients with prior myocardial infarction, transient ischaemic attack or peripheral vascular disease. Multivariate analyses showed associations to be independent only in the myocardial infarction group, after adjustment for fibrinogen and protein C concentration. Another study[3] examined the predictive value of haemostatic factors for sudden death in patients with stable angina pectoris. Factor VIII coagulant was found to be a univariate predictor of sudden death in this population. In the Northwick Park heart study, mean factor VIIIc concentrations were significantly higher in patients who died of ischaemic heart disease compared with survivors.[4]

Activated protein C resistance has recently emerged as an important cause of venous thrombosis,[5] and in 90% of cases it is associated with a single point mutation in the factor V gene (FVQ 506 or factor V Leiden), which removes an important cleavage site for activated protein C. Despite this prothrombotic effect, the relation among APCR, factor V Leiden, and myocardial infarction remains unclear. A functional relation has been reported to exist between APCR and factor VIII.[6] Therefore, raised factor VIII may explain APCR and the increased thrombotic risk in patients without factor V Leiden. More recently it has emerged that impaired function of the protein C pathway, including thrombomodulin expression and function, as well as the Leiden mutation, contributes to the increased risk of myocardial infarction.[7 8]

The cases presented here illustrate the association between raised plasma factor VIII and acute myocardial infarction. They constitute an unusual group of patients with myocardial infarction as they are all female and suffered their first thrombosis at a young age. Case 1 was also unusual because subsequent coronary angiography showed no occlusion, significant stenosis or other evidence of atheroma. Case 3 is of interest because the raised factor VIII was found before myocardial infarction; therefore, it could not have been a consequence of the infarction. Furthermore, it was associated with APCR in the absence of the factor V Leiden mutation. Of particular interest in this case is the evidence of rapid development of extensive coronary thrombosis (more than one coronary artery branch involved, extensive myocardial infarction, and rapid development of Q waves) without plaque rupture but with microembolism, indicating a powerful prothrombotic state.

These cases provide further evidence for the association of factor VIII with sudden thrombotic events. There may be a causal relation between raised factor VIII and acute thrombotic events, such as myocardial infarction, even in those without significant underlying atheromatous disease.

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