Epstein’s syndrome: case report and survey of the literature

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Summary: A diagnosis of Epstein’s syndrome was made in a young female with congenital macrothrombopathic thrombocytopenia, a nephropathy and mild sensorineural deafness. Previous case reports of this rare disorder are briefly reviewed and attention is drawn to the frequent association between inherited thrombocytopenia and renal disease.

Introduction

Alport’s syndrome in its classical form is characterized as a dominant inherited disorder in which nephritis is associated with high tone sensorineural deafness.¹ ² Other rare abnormalities occasionally recognized in affected patients include polineuropathy, hyperprolinaemia and ichthyosis³ and ocular defects such as retinitis pigmentosa, cataracts, lenticonus and spherophakia.⁴ In 1972, Epstein and co-workers⁵ described four patients from two kindreds who had hereditary nephritis and nerve deafness indistinguishable from Alport’s syndrome in association with macrothrombopathic thrombocytopenia. In this report we describe the presentation and clinical course of a young female with this rare disorder.

Case report

A 22 year old female was initially diagnosed as suffering from idiopathic thrombocytopenia at age 5 years following an uncomplicated fracture of the left femur. There was a history of easy bruising and recurrent epistaxis from birth and several episodes of otitis media in infancy. Further investigation of the thrombocytopenia at the age of 13 years showed platelet counts of 12–20 x 10⁹/l; bizarre giant forms were recognized on the blood film (Figure 1). The bleeding time was prolonged at 13 minutes and the prothrombin consumption index slightly increased at 24%. Other coagulation tests including thrombin clotting time, one stage prothrombin time, kaolin cephalin clotting time and the thromboplastin screening test were normal. Serum immunoglobulins and isohaemagglutinin titres were normal and the antinuclear factor antibody and direct Coombs’ test were negative. Because of the severe thrombocytopenia, platelet aggregation studies could not be performed. A bone marrow aspirate revealed normal to increased numbers of megakaryocytes, many of which showed abnormal morphology with peripherally localized, condensed nuclei and poorly granular cytoplasm. There was no evidence of platelet budding.

From the age of 14 years she suffered recurrent urinary tract infections and when more fully investigated at the age of 18 years, microscopic haematuria and heavy proteinuria (12.5 g/l) was recognized. On clinical examination she was normotensive with no peripheral oedema or abdominal masses palpable. The plasma urea was 2.6 mmol/l and an intravenous pyelogram was normal. At this time she also complained of difficulty in hearing in both ears associated

Figure 1 Photomicrograph showing giant platelet (arrow) in peripheral blood (Wright’s stain, magnification × 1000).

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with tinnitus, and audiometry demonstrated a mild, symmetrical sensorineural deficit. A diagnosis of Epstein's syndrome was made on the basis of the macrothrombopathic thrombocytopenia, nephropathy and sensory deafness. Both parents and two siblings had normal platelet counts and morphology and there was no evidence of renal disease or hearing disorder in the family.

At 21 years of age she was admitted with epigastric pain of 5 days' duration which radiated to the back and was associated with vomiting. There was no history of excessive alcohol intake and she was taking no medication. Apart from epigastric tenderness there were no abnormal physical findings. The serum amylase was elevated at 1550 U/dl and serum bilirubin increased at 47 μmol/l (mainly direct). The serum alkaline phosphatase was 91 IU/l, serum albumin 27 g/l, corrected calcium 2.34 mmol/l and glucose 4.7 mmol/l. An abdominal ultrasound showed an oedematous pancreas but no pseudocyst formation. The gall bladder wall was thickened but no calculi were visualized in the biliary tree. Both kidneys were highly echogenic and slightly irregular in contour. A diagnosis of acute pancreatitis was made which settled on conservative treatment. A subsequent oral cholecystogram showed poor gall bladder contraction after a fatty meal but was otherwise normal. One month after the initial episode, she suffered a mild recurrence of the pancreatitis and recovery was again uncomplicated. Currently the serum creatinine is 77 μmol/l with a creatinine clearance of 106 ml/min. Heavy proteinuria persists (10 g/24 h) but the serum albumin has increased to 40 g/l. Neither endoscopic retrograde cholangiopancreatography nor renal biopsy have been felt justifiable in view of the severe thrombocytopenia.

Discussion

The association of inherited macrothrombopathic thrombocytopenia, nephritis and sensorineural deafness was first described by Epstein in 1972 and five more recent reports in the American literature indicate that this rare triad is a distinct clinical entity.\(^1\)\(^-\)\(^5\) In common with the majority of previous cases, the platelet defect in the present patient was diagnosed at an early age and preceded by some years the development of the nephropathy and mild hearing deficit. Analysis of the small number of pedigrees reported suggests that Epstein's syndrome is transmitted by autosomal dominant inheritance.\(^6\)\(^,\)\(^7\) If correct, the absence of phenotypic abnormalities in the immediate family members of our patient indicates that her disease resulted from a new mutation.

A single kindred in which affected individuals showed features of Epstein's triad accompanied by cataracts and cytoplasmic inclusions in neutrophils and eosinophils has been described.\(^8\) In addition, there is one report of a patient with nephritis, deafness and macrothrombocytopenia in association with cystic medianecrosis of the ascending aorta and malformation of the aortic valves.\(^9\) However, acute relapsing pancreatitis has not been previously recognized as a complication of Epstein's syndrome. Non-invasive radiological investigations of the biliary tract in our patient suggested that the pancreatitis was most likely related to a coexistent chronic cholecystitis and we suspect that this probably represents a chance association. However, the possibility that the biliary and/or pancreatic pathology is in some way causally related to the underlying gene defect in this multisystem disorder cannot be entirely excluded.

In the original report by Epstein and colleagues, the platelet defect was characterized by giant forms with abnormal ultrastructure and impaired function in terms of decreased glass adherence and diminished aggregation in response to ADP, collagen and adrenalin. Similar observations have been made in two more recently described cases\(^6\)\(^,\)\(^7\) and it has been suggested that the giant platelets are derived from abnormal megakaryocytes in which there is failure of the demarcation membrane system.\(^7\) Normal platelet budding is impaired and the megakaryocytes undergo degeneration and cytoplasmic fragmentation. The survival of the macrothrombocytes in vivo has been reported to be normal\(^8\) and transfused random donor platelets correct the prolonged bleeding time and produce significant platelet increments.\(^5\)

The renal pathology in Epstein's triad is indistinguishable from Alport's syndrome and consists of sclerosing and proliferative glomerulonephritis with mesangial cell expansion, interstitial nephritis and fibrosis.\(^5\)\(^,\)\(^6\)\(^,\)\(^8\) Presentation with haematuria and proteinuria is typical and progression to end stage renal failure between the third and fifth decade frequently ensues. Despite the bleeding tendency, however, the feasibility of renal transplantation has recently been documented.\(^10\)

A number of investigators have drawn attention to the association between nephritis and other types of familial thrombocytopenia including the May-Hegglin anomaly,\(^11\) familial immune thrombocytopenia\(^12\) and the Wiskott-Aldrich syndrome.\(^13\)\(^,\)\(^14\) These disorders have been broadly categorized as so-called 'thromboenral syndromes' but since their inheritance patterns are variable and both the renal pathology and platelet defects are heterogeneous, the explanation for this association remains obscure. Nevertheless, these reports suggest that, in clinical practice, care should be taken to exclude an associated nephropathy in any case of inherited thrombocytopenia.
References

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