

Short reports

Liver failure and Epstein-Barr virus infection

N J SHAW AND J H C EVANS

Department of Paediatrics and Child Health, St James's University Hospital, Leeds

SUMMARY A 5 year old boy developed liver failure secondary to infection with Epstein-Barr virus. He was subsequently shown to have a partial C4 complement deficiency. The importance of considering Epstein-Barr virus as a cause of fulminant hepatic failure and the need to assess immune state in such an event is emphasised.

Case report

A 5 year old boy was referred because of increasing jaundice and confusion. He had been unwell for four days, initially he was just listless but he subsequently lost his appetite and started vomiting. On the morning of referral he was vomiting profusely and complained of abdominal pain, by the afternoon he was delirious and jaundiced. There was nothing of note in his medical or family history. He had had no contact with hepatitis but had been on a school trip to a farm one week earlier. He had received no blood transfusions nor had he taken any drugs recently. On arrival at hospital he was drowsy and responded only to painful stimuli (grade IV coma). He was restless and had bite marks on his arms (self-inflicted). His pupils were dilated but reacted to light; his fundi were normal. He had generalised hyper-reflexia and extensor plantar responses. He was deeply jaundiced with hepatic fetor, he was also dehydrated and had a blood pressure of 125/75 mm Hg and a temperature of 36.9°C. Neither his liver nor his spleen were palpable. He had no lymphadenopathy and his tonsils were normal.

The results of investigations were as follows: prothrombin ratio 5.2; thrombin time 18 seconds (control 14 seconds); kaolin cephalin clotting time 43 seconds (control 42 seconds), bilirubin concentration 594 µmol/l (direct bilirubin 301 µmol/l); alanine aminotransferase activity 5560 IU/l; alkaline phosphatase activity 310 KAU/l. Blood glucose was 4.3 mmol/l and plasma proteins were normal. His haemoglobin was 109 g/l, white cell count $32.6 \times 10^9/l$, (83% neutrophils, 13% lymphocytes), platelets $294 \times 10^9/l$, reticulocytes 7.8%; the blood film was normal and a direct Coombs test gave a negative result.

His serum sodium concentration was 136 mmol/l, potassium 5.3 mmol/l, bicarbonate 17 mmol/l, urea 11.7 mmol/l, and creatinine 183 µmol/l. Microscopy of the urine showed the presence of red cells and red cell casts and urinalysis gave a positive result for protein (++) , blood (++++), and bilirubin (a large amount); the urobilinogen was normal.

A Paul-Bunnell test, Monospot test, and test for serum antibodies to Epstein-Barr virus all gave positive results (table). Serum C3 concentration was 0.86 g/l (normal range 0.55-1.20), C4 0.14 g/l (normal range 0.2-0.5), and C4 functional activity was 50% of normal as assessed by haemolytic assay.

The following investigations gave normal results: lumbar puncture; blood and urine culture; hepatitis B surface and core antigen tests; antibody titres to hepatitis A, cytomegalovirus and leptospira; analysis of immunoglobulins; and ultrasound examination of the liver and spleen.

He was managed on the intensive care unit. His fluids were restricted to 1000 ml/m²/day of 10% glucose. He received fresh frozen plasma to improve

Table Results of tests for serum antibodies to Epstein-Barr virus

	At presentation	Time after presentation			
		2 Months	4 Months	9 Months	12 Months
IgM to Epstein-Barr viral capsid antigen	+	-			
IgG to Epstein-Barr viral capsid antigen	+	+			
IgM to Epstein-Barr virus nuclear antigen	-	-	-	+ weak	+ weak

his prothrombin ratio, vitamin K₁, cimetidine, lactulose, and oral neomycin. Ampicillin was started to cover the possibility of leptospirosis before the result of the Monospot test was known. Interestingly, he did not develop an 'ampicillin rash'.

For 24 hours he was in grade IV hepatic coma and received intravenous mannitol when his pupils became unreactive to light. He then improved rapidly with decreasing jaundice and an improved level of consciousness. Four days after presentation he was fully conscious and his serum bilirubin was 175 µmol/l, prothrombin ratio 1.4, and alanine aminotransferase 1400 IU/l. After two weeks his serum bilirubin was 29 µmol/l. His alanine aminotransferase was 39 IU/l after five weeks. One year after presentation he remains entirely well, but his C4 concentration and functional activity remain low.

Discussion

This 5 year old boy presented with a rapid onset of hepatic failure with evidence of glomerulonephritis shown by the presence of red cell casts in the urine. This was shown to be secondary to infection by Epstein-Barr virus as evidenced by a positive Monospot test and the presence of IgM and IgG antibodies to the viral capsid antigen. Other causes of liver failure were excluded. There were no clinical features to suggest infectious mononucleosis and he did not have an atypical lymphocytosis. He has a complement C4 deficiency that may account for the severity of his illness.

Numerous complications have been reported in association with infectious mononucleosis but severe jaundice with liver failure is very rare. Although raised aminotransaminase activities are found in roughly 80% of patients with infectious mononucleosis, clinical jaundice occurs in 5% only.¹ There are only 12 reported cases of hepatic failure secondary to Epstein-Barr virus infection with only one survivor. The fatal cases are reviewed by White and Juel-Jensen.¹ The sole survivor was a 25 year old man who developed signs of hepatic coma 16 days after presentation with a maximum serum bilirubin concentration of 170 µmol/l.² He recovered after being in stage III coma for two days; his recovery was attributed to the use of high dose steroids. All but one of the reported cases had typical clinical features of infectious mononucleosis. It is well known, however, that primary infection with Epstein-Barr virus often occurs in children without symptoms or typical clinical features.

It has been suggested previously that failure to develop atypical mononuclear cells during Epstein-Barr virus infection may represent a defect in cell mediated immunity.³ There have been several reports of cases of fatal infectious mononucleosis where an immune defect has been identified, the most well known being those individuals with the X linked recessive lymphoproliferative syndrome (Duncan's disease). A severe illness consequent to Epstein-Barr virus infection in an individual with a complement deficiency, however, has not previously been reported. Individuals who are deficient in C4 may have an impaired immune response to viral antigen that could account for the severity of the illness experienced by this child.⁴

It is of concern that individuals with C4 deficiency have been reported to develop systemic lupus-like illness in later life⁵ but at present the child reported here is well with no apparent sequelae from the liver failure or Epstein-Barr virus infection.

It seems remarkable that he survived considering the severity and rapid progression of his illness. It is felt that only 15–25% of children will survive grade IV hepatic coma.⁶

We report this case in order to indicate the importance of considering Epstein-Barr virus as a cause of hepatic failure and the need to assess immune state if this is the case.

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Correspondence to Dr NJ Shaw, Department of Paediatrics and Child Health, St James's University Hospital, Leeds LS9 7TF.

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