

single family, and this point was stressed during the counselling. HLA genotyping may therefore have a practical clinical application in ascertaining the distribution of the 21-hydroxylase deficiency gene as the basis for genetic counselling.

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Correspondence to Dr M O Savage, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

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Hepatic cellular injury during varicella

MARTIN G MYERS

Department of Pediatrics, the University of Iowa Hospitals, Iowa City, USA

SUMMARY Serological evidence for hepatic cellular injury may occur during uncomplicated varicella. The magnitude of abnormalities may be helpful as a guide in the management of children with progressive varicella or varicella-associated Reye's syndrome, but liver function tests may be in the normal range. Viraemia was not detected during the acute stage of varicella-associated Reye's syndrome.

Susceptible children who are immunologically compromised by disease or treatment are at risk of developing progressive varicella if exposed to varicella-zoster virus. Serological evidence of hepatic cellular injury has been used to corroborate the clinical impression of progressive infection in such patients. In addition, hepatic cellular injury is a diagnostic criterion for Reye's syndrome¹ which may complicate varicella. Because varicella is a self-limited childhood exanthem, evidence of hepatic cellular dysfunction is not generally sought in the

normal child undergoing a typical course of infection. However, recent reports suggest that chemical hepatitis may occur during apparently uncomplicated varicella.²⁻⁴ Therefore, normal children with varicella, children at risk of developing progressive varicella, and children with Reye's syndrome complicating varicella were evaluated for serological evidence of hepatic cellular dysfunction. Because progressive varicella has been associated with viraemia during exanthem,⁵ children with Reye's syndrome were also examined for the occurrence of viraemia during the early stages of encephalopathy.

Materials and methods

After informed consent had been obtained, 75 patients with varicella, confirmed by the recovery of varicella-zoster virus from vesicle fluid in human fibroblast tissue cultures or by the demonstration of a 4-fold rise in membrane fluorescence antibody titre,⁵ were evaluated for serological evidence of

hepatic cellular injury. All, except 9 children with Reye's syndrome, were evaluated during the first 4 days of exanthem. Siblings of patients with Reye's syndrome were excluded. Twenty-nine children without underlying disease had a course typical of varicella. Thirty-four patients at risk of developing progressive varicella, because of underlying disease or immunosuppressive therapy, were evaluated and 16 of them were considered to have had a progressive course of infection.⁵ None of the children with progressive infection had evidence of hepatic cellular dysfunction and encephalitis without the clinical involvement of other organ systems.

An additional 11 children who met the criteria of Reye's syndrome¹ complicating varicella were evaluated for evidence of hepatic cellular injury and for the presence of viraemia during the first 3 days of encephalopathy, representing the 4th to 16th day of exanthem. Only 2 of these children were examined

during stages of vesicle formation. Children with Reye's syndrome had no evidence of underlying disease and had not received immunosuppressive therapy before the onset of encephalopathy.

Serum aspartate transaminase (AST),⁶ alanine transaminase (ALT),⁷ lactic dehydrogenase (LDH),⁶ alkaline phosphatase (AP),⁶ and total bilirubin levels⁶ were assayed at the time of illness. On some patients, AST and ALT were assayed⁷ on serum stored (-20°C) for between 6 months and 5 years. Similar AST and ALT results were obtained on 5 sera evaluated by both methods. Plasma ammonia was assayed⁸ on heparinised venous blood stored on ice for 20 minutes before assay. Buffy coat cultures were performed in newborn human fibroblast tissue cultures as previously described.⁵

Results

Serological evidence for hepatic cellular dysfunction

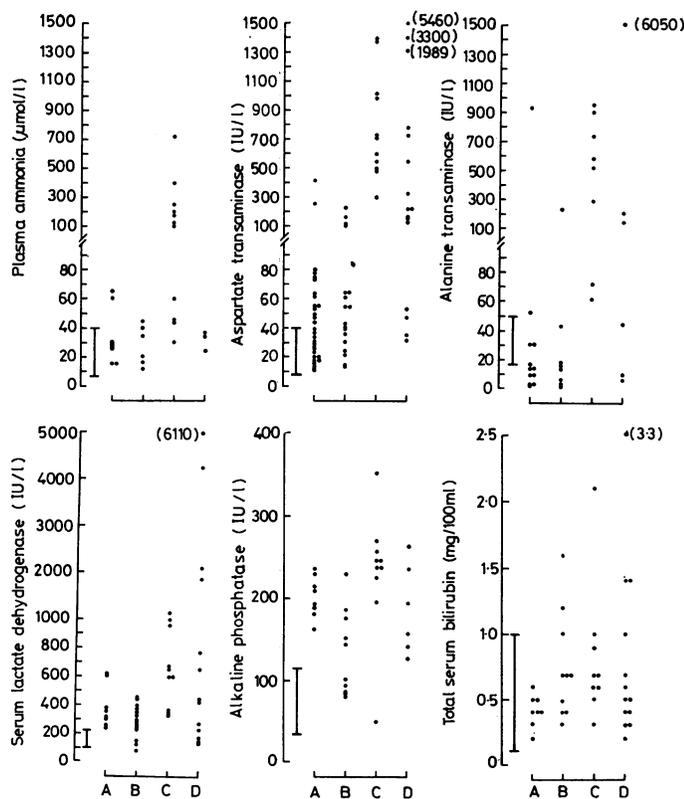


Figure Liver function tests during varicella.

The normal ranges of values are bracketed on the ordinates.
 (A) Normal children, typical varicella.
 (B) 'At risk' children, typical varicella.
 (C) Normal children, varicella-associated Reye's syndrome.
 (D) 'At risk' children, progressive varicella.

was detected in patients undergoing a typical or an unusual course of varicella (Figure). Most children with progressive varicella-zoster virus infection and those with Reye's syndrome had raised serum enzymes and plasma ammonia levels. Although the degrees of apparent hepatic cellular abnormality in these patients exceeded those in children undergoing a typical course of varicella, some of the latter children also had serological evidence of hepatic cellular injury during their acute vital illness. Thus, about one-third of the normal children experiencing uncomplicated varicella had slightly raised AST values and 2 had pronounced increases, 2 children undergoing uncomplicated varicella had raised ALT values, and almost all children had high AP and LDH values. Although cutaneous vesicles were not enumerated in all patients, the serum LDH appeared to correlate with the degree of dermal injury in patients with typical varicella. High levels of plasma ammonia appeared to be correlated in most patients with increases in both AST and ALT.

None of the 11 patients with varicella-associated Reye's syndrome was viraemic during the first 3 days of encephalopathy.

Discussion

Serological evidence of hepatic cellular dysfunction may be detected during the course of typical varicella in normal and immunologically modified patients as well as in those experiencing an unusual course of infection. However, the magnitude of abnormalities in those experiencing progressive varicella or Reye's syndrome is greater than that seen in patients with typical varicella. Although some of the serological abnormalities may have derived from cells other than the hepatocyte, the high AST and plasma ammonia values seen in patients with typical varicella imply specific hepatic cellular injury. Because the plasma ammonia level may be raised in normal children with varicella, increases in AST, ALT, bilirubin, and AP also probably reflect hepatic cellular injury during varicella. However, increases in the total serum LDH in patients with typical varicella may reflect the degree of cutaneous involvement during varicella,² although fractionation of the LDH might distinguish the site of cellular injury.

The failure to demonstrate viraemia in patients with varicella and encephalopathy due to Reye's syndrome supports the thesis that the pathophysiology of Reye's syndrome is different from that of progressive varicella-zoster virus infection with

hepatic and central nervous system involvement. Alternatively, viraemia may precede the onset of encephalopathy in Reye's syndrome. However, in 5 previously reported⁵ patients with progressive infection affecting the central nervous system, viraemia occurred simultaneously with encephalopathy, and in one child persisted for 15 days.

In the absence of histological studies, it is possible only to speculate whether the hepatic histology in children undergoing uncomplicated varicella is similar to that observed in children with either progressive infection or Reye's syndrome. Although serological evidence of hepatic cellular injury may be a guide in the management of children suspected of having progressive varicella or Reye's syndrome, it may be within the normal range in these children and may be abnormal in children experiencing a 'typical' course of varicella infection.

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Correspondence to Dr M G Myers, Children's Hospital Medical Center, Elland and Bethesda Avenue, Cincinnati, Ohio 45229, USA.

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