Clinical problems in hepatitis in childhood King's College Hospital experience 1970-73

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IN arranging the programme for this meeting we have been conscious of the problems encountered in the investigation and management of children referred to the Department of Child Health and Liver Unit, King's College Hospital, with acute and chronic hepatitis. Two areas of particular concern are the frequent failure to establish the cause of the hepatitis and the difficulty in assessing the value of therapy. We do not plan to summarize our experience but to highlight some of the major clinical problems in the hope that during the course of the meeting some progress can be made in clarifying them.

The first group to consider are those infants with the Neonatal Hepatitis Syndrome or its sequelae, of which we have seen approximately one hundred cases in the last 3 years. Some of the outstanding problems that these infants present are listed in Table 1. A

TABLE 1. Problems in neonatal hepatitis syndrome

Non-laparotomy diagnosis of biliary atresia
Surgical management of biliary atresia
Aetiological diagnosis
Assessment of prognosis in neonatal hepatitis
Therapy of neonatal hepatitis

major clinical difficulty is to distinguish those who require laparotomy to exclude surgically correctable biliary atresia or a choledochal cyst, knowing that laparotomy should be avoided in hepatitis (Thaler and Gellis, 1968) and that for the majority of patients with biliary atresia surgery is unhelpful (Alagille *et al.*, 1969). Standard liver function tests are of little value but percutaneous liver biopsy (Brough and Bernstein, 1969), ¹³¹I-Rose Bengal excretion test (Maksoud *et al.*, 1971), determination of serum lipoprotein-X concentrations (Poley *et al.*, 1972), and serum bile salt patterns (Javitt *et al.*, 1973), have each been claimed to distinguish infants with patent extrahepatic biliary tracts from those with biliary atresia. Considerable experience is required for the correct interpretation of liver biopsies. The ¹³¹I-Rose

Bengal excretion test may give false negative results when there is urinary contamination of faeces, and false positive results when there is complete cholestasis. The last two techniques mentioned have not been fully evaluated.

Surgical treatment of biliary atresia is far from satisfactory. Biliary drainage via the gall bladder can be established in less than 10% of cases (Alagille *et al.*, 1969). For a minority of the remainder, biliary drainage may be affected by a hepatic portoenterostomy (Kasai *et al.*, 1968), but it has yet to be shown that this influences prognosis (Kobayashi *et al.*, 1973).

Although we have systematically and prospectively studied our cases (Porter *et al.*, 1972) for known genetic, infectious, or other exogenous causes (Mowat, 1972) in over 80% of cases none was identified. If it is true that 25% die of liver disease in infancy, 50% go on to chronic liver disease, while 25% make a complete recovery (Silverman, Roy and Cozzetto, 1971), what are the factors which determine the outcome? Is it the cause or the response in the infant, as would seem to be the case in, for example, genetic deficiency of Alpha-1-antitrypsin? Will systematic investigation of, for example, immunological responses or serum bile salts be helpful in trying to identify those who recover spontaneously and those who might require therapy?

When we consider therapy, there are even greater problems. Not one of the twelve suggested forms of treatment for Neonatal Hepatitis Syndrome listed in Table 2 has been subjected to controlled trials. Are any to be seriously advised for our patients? Corticosteroids have their advocates (Kaye, 1969) but an equal number of paediatricians seem to be sufficiently convinced that they are without value in this situation so that we often have difficulty in getting patients admitted to a randomly allocated controlled trial (Mowat, Stroud and Williams, 1973) because the referring paediatrician is firmly of one or other viewpoint. Can we in fact define a group of sufficient homogeneity, particularly with regard to prognosis, to resolve this controversy by a properly conducted controlled trial?

TABLE 2. Suggested therapy for neonatal hepatitis

(1950-73: English Language Literature)

Milk—intramuscular injection
 Dimercapto-propyl-phthamic acid
 Corticosteroids
 A.C.T.H.
 Methoxyphenyl-dithio-cyclopentene
 Dietary substances—unidentified
 Amino acids
 Vitamin B12
 Mud poultices over liver
 'Neoperhepar'
 Immunosuppressives
 Cholestyramine
 Phenobarbitone

FIG. 1. Schematic illustration of the different time course of changes in serum aspartate transaminase levels (i.u./l.) and prothrombin times (sec) during the course of fulminant hepatitis with encephalopathy and spontaneous haemorrhage in a 6-year-old girl treated with corticosteroids and fresh frozen plasma. —, aspartate transaminase; — —, prothrombin time.

FIG. 2. Serum bilirubin (mgm/100 ml) and alkaline phosphatase (i.u./l.) values from the same patient showing yet another pattern of change. —, serum bilirubin: total; ●, serum bilirubin: direct reading; — —, serum alkaline phosphatase.

The second group of children that I wish to consider are much less numerous but cause major clinical difficulties. These are children with acute hepatitis complicated by encephalopathy and spontaneous haemorrhage. Figures 1 and 2 show schematically some of the disturbances of liver function in one of six such children admitted in the last 18

months. Encephalopathy had occurred on admission and on two subsequent occasions in the second and third hospital month. Orthodox treatment for fulminant hepatitis was given, together with corticosteroids in the form of prednisolone in a dose of 40 mg/24 hr for the first 6 weeks and reduced over a 4 week period to 10 mg/24 hr. The serum aspartate transaminase level was very high early in the hospital course but fell rapidly. It appeared to rise slightly when the steroid dosage was reduced. To what extent these changes were produced by prednisolone is difficult to assess. One is aware that the use of corticosteroids in this situation is experimental. Most authorities (Cook and Sherlock, 1965; Williams, 1972; Saunders *et al.*, 1972) consider that their efficacy is dubious but faced with a child in such a state and with even one report suggesting that they are of value in hepatitis (Katz *et al.*, 1962), it is difficult to withhold them. A major problem was failure of hepatic synthesis of clotting factors without evidence of disseminated intravascular coagulation. Spontaneous bruising occurred until fresh frozen plasma transfusions were started early in the hospital course. These had to be continued regularly for 3½ months. Would there have been advantages in using plasma concentrates with higher concentrations of some clotting factors and less sodium? Would heparinization have helped (Rake *et al.*, 1971)? In Fig. 2 the abnormalities of liver function tests indicate the severe cholestasis which persisted in spite of the fall in serum transaminase levels shown in Fig. 1. This single case study may indicate that corticosteroids have some beneficial effect on hepatocellular integrity as reflected in the serum transaminase levels, but they can hardly be claimed to have aided hepatic excretion, nor to have improved the synthesis of clotting factors. Cholestyramine was given after the first 10 weeks in hospital, but what part, if any, it played in the remission of cholestasis, is difficult to assess. The patient is now clinically well.

No cause was found for this child's hepatitis, nor was there a history of exposure to drugs, or contact with known cases of hepatitis. In other instances we have observed transient skin rashes which have suggested a viraemia but have never substantiated this. In one child the hepatitis might have been drug induced but this patient also showed a rise in serum antibody titre to cytomegalovirus. If hepatitis A is the cause in the remainder, why does it follow such a fulminant course in these children? Is it variability in the hypothetical virus A? Is it dose related? If the reason is in the child, what parameters can be studied?

When we consider our experience with chronic hepatitis, with or without cirrhosis, we have the same problem. Aetiology undetermined in over 80% of cases, pathogenesis and prognosis uncertain, and no

therapeutic agent of proven efficacy. Even when we do identify a possible cause, management is controversial. We recently have had under our care a 3-year-old boy who presented with a 5-month history of abdominal distension and hepatosplenomegaly and had the pathological features of chronic aggressive hepatitis associated with hepatitis B antigenaemia. Because of the pathological diagnosis we have treated this child with corticosteroids. His serum transaminases have coincidentally fallen from levels of approximately ten times normal to levels which are now one and a half times normal. After 9 months of therapy he still, however, has hepatitis B antigen in the peripheral blood. Have we caused the antigen to persist by using corticosteroids? Would immunoglobulin with a high titre of antibody to hepatitis B antigen have had any therapeutic role in this situation?

We hope that this meeting will serve a number of functions. With the help of the many experts we have enticed here, both speakers and guests, it should allow us to evaluate the significance of advances in some aspects of hepatitis in which there has been much recent growth in knowledge. In my review of our clinical experience of these three forms of hepatitis in infancy and childhood I have indicated how frequently the cause is undetermined, pathogenesis uncertain, and factors influencing prognosis are largely unknown and emphasized our concern that until adequately controlled trials of therapy are performed, we may do our patients as much harm as good. We hope, therefore, that this meeting will also indicate how these pressing clinical problems may be more clearly defined, investigated and resolved. Most importantly, the meeting should provide a stimulus for both clinical and laboratory research in paediatric liver disease.

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