ASPECTS OF VIRAL HEPATITIS IN INFANCY AND CHILDHOOD

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The virological and pathological features of viral hepatitis reported in earlier chapters apply equally in children and in adults. The liver in health is a complex but very efficient organ containing many types of cells all carefully positioned and orchestrated to perform a host of functions with a considerable reserve capacity and the ability to recover completely from many forms of injury. There are in infants and young children a number of differences which may modify the liver's response to infection or other injury. The liver acinus is similar to that of the adult but instead of the hepatocytes being arranged in plates which are one cell thick the plates are two cells thick which limit the transfer of material across the hepatocyte membrane into and out of plasma. This arrangement persists throughout the liver until two years of age but may still be found even at five years (Mowat, 1979). In early infancy the distribution of blood within the liver may be less homogeneous than in the older child or adult. There are important associated physiological "handicaps". The most familiar is the so-called "physiologic jaundice" which persists up to 10-14 days in healthy infants and is in part due to ineffective hepatic function (Maizels, 1981).

Less well known is the reduction in the liver's ability to remove bile salts from serum as effectively in infancy as in adult life. This handicap persists in all infants of up to 12 months of age but can still be found in some children up to six years of age (Balistreri *et al.*, 1981). Even with these handicaps hepatitis in infancy may be both asymptomatic and anicteric. In this age group the liver's response to injury is characterised by an increased propensity to giant cell transformation, bile duct reduplication and perhaps an increased tendency to deposit fibrous tissue (Portmann *et al.*, 1976).

Table 1. — *Viral causes of hepatitis in infancy.*

Hepatitis B virus
Non-A, non-B hepatitis
Cytomegalovirus
Rubella
Herpes virus hominis
Coxsackie B virus
Adenovirus
Echo virus 11
Varicella-Zoster

In comparing the infant with the adult we must also consider the immune system. There seems to be every reason to believe that by 20-24 weeks of gestation, both humoral and cellular immunity are effective. The full-term infant is lacking in immunological experience. He is not immune deficient and can raise an appropriate cellular and humoral immune response. The fetus infected very early for example, by rubella virus at 12-16 weeks, may develop immune tolerance and go on excreting the virus for a long period post-natally (Frommel and Good, 1971). Finally, it is important to remember that the competence of the immune system is not constant. It may be very severely affected by intercurrent infection, particularly by measles or the Ebstein-Barr virus.

Because of the infant's immune inexperience, we see many causes of viral hepatitis in early infancy (table 1). Such infection usually occurs as part of a generalised infection in which the liver is often less severely damaged than other organs. In parts of the world where hepatitis B or non-A, non-B hepatitis is common, infants may acquire this infection and present with hepatocellular disease without signs of other organs being involved. Viral hepatitis type A has not been implicated in causing hepatitis in infancy, the majority of infants presumably being protected by antibody derived from their mothers (Skinhøj *et al.*, 1977). Clinically such viral hepatitis is often indistinguishable from the other forms of hepatitis syndrome in infancy arising secondary to genetic abnormalities or bile duct lesions. Cytomegalovirus infection may occur in any of these disorders, as well as in normal infants and from the point of view of clinical management is probably best disregarded. It should be stressed that in only about 10-15% of infants presenting with conjugated hyperbilirubinaemia can an infective agent be isolated. Infections such as syphilis, urinary tract infection, septicaemia and toxoplasmosis, are of greater clinical importance than viral infection since effective treatment is available.

In extrahepatic biliary atresia the extrahepatic bile ducts are progressively destroyed by inflammatory process which initially causes degeneration of the biliary endothelium, followed by inflammatory cell infiltrate and increasing fibrosis in the area resulting initially in complete blockage of the extrahepatic ducts and followed by marked intrahepatic fibrosis and, ultimately, death from cirrhosis. The aetiology of this disorder is unknown. There is experimental evidence that suggests that such pathological changes can be caused in weanling mice by certain strains of reovirus. Preliminary attempts to implicate this virus in hepato-biliary disease in man have been promising (Bangura *et al.*, 1980).

Hepatitis A in childhood

The development of serological markers for hepatitis A, i.e. the specific IgM and IgG antibodies to hepatitis A virus, has allowed studies which largely confirm earlier epidemiological observations (Hopper *et al.*, 1977).

Hepatitis A virus is a 27 nm RNA-containing member of the enterovirus sub-group of Picornavirus. Infection occurs via the oral route. Hepatitis A virus appears in stools within 7-10 days of exposure and is present in large amounts until just before the onset of the hepatitis. As the hepatitis becomes evident the concentration in the stools falls dramatically. Low concentrations may persist for a few weeks, particularly if liver damage is severe.

IgM antibodies specific to HAV appear at 1-3 weeks after exposure and persist for 4-10 weeks (Rakela and Mosley, 1977). Specific IgG antibodies become detectable shortly after the IgM antibodies and persist giving life-long immunity, except perhaps with a massive virus inoculation. Only one serotype of hepatitis A has been identified in different geographical regions, in sporadic cases of hepatitis A and in experimentally and naturally infected chimpanzees. Evidence is accumulating that there may be some antigenic strain differences, a hepatitis virus or viruses which epidemiologically resemble hepatitis A virus may be responsible for a substantial number of cases of acute hepatitis in the Indian sub-continent. These are preliminary observations and at present it seems that if a subject has once been infected by hepatitis A virus they will have life-long immunity (Stakhanova *et al.*, 1979; Wong *et al.*, 1980).

In most parts of the world this is very much a disease of childhood. More than 50% of cases are asymptomatic. More than 90% are anicteric. There is much under-recording. The incidence is essentially unknown. There is no carrier-state. Perpetuation of hepatitis A infection depends on a reservoir of inapparent cases.

The incidence of antibodies to HAV increases with increasing age and with decreasing socio-economic settings which favour the dissemination and ingestion of enteroviruses (Dienstag, 1980).

DIAGNOSIS

The diagnosis is established by the determination of an IgM antibody response early in the course of the disease. If such studies are not available, the diagnosis can be established by the epidemiological setting and by the exclusion of other causes of acute hepatitis in this age-group, particularly hepatitis B, infectious mononucleosis and cytomegalovirus. It is particularly important to remember that occasionally Wilson's Disease may present in a similar fashion. It has to be excluded by examining the patient for Kayser-Fleischer rings and by measuring the serum caeruloplasmin and urinary copper. Chronic active hepatitis, another treatable disorder should be excluded by determining the serum immunoglobulins and tissue autoantibodies.

The most important investigations in assessing the severity of liver disease are the prothrombin time, the serum albumin and transaminase values. There is no effective treatment. Should features of fulminant hepatic failure develop, intensive care is necessary in a unit specialising in the management of this disorder (Jenkins and Williams, 1980).

PREVENTION

There is as yet, no vaccine for hepatitis A. 200 mg of human normal immunoglobulin injection B.P. produces effective passive immunisation in children up to ten years of age with 500 mg in older children. The effects last for approximately 4-6 months. It is recommended for family contacts and in epidemics in Institutions in which good hygiene conditions are difficult to achieve. It is particularly important in epidemics to try to block faecal-oral spread from contacts of all recognised cases by scrupulous attention to hand-washing before meals and after defaecation.

Viral Hepatitis type B

Virological, pathological and serological aspects of this virus and the body's response to it have been discussed. I wish to stress the following points:

1) the duration of antigenaemia in acute hepatitis may range from a few hours to months;

Table 2. — *Pathological response to hepatitis V virus in childhood.*

Asymptomatic development of anti-HBs
Acute hepatitis
Papular acrodermatitis
Acute hepatitis proceeding to chronic hepatitis
Chronic liver disease
Carrier-state healthy
Carrier-state with immune disorders, e.g. Down's Syndrome, leukaemia, renal failure
Immune complex diseases (renal, peri-arthritis, pericarditis)
Hepatocellular carcinoma

2) following the clearance of hepatitis B surface antigen or hepatitis Be antigen, there is frequently a "window" period in which the antibody to these antigens is also undetectable in the serum;

3) the best serological marker for past hepatitis B infection is anti-HBc.

Two major enigmas concern hepatitis B infection. The first is the observation that a proportion of subjects fail to develop an effective antibody response. The second is the varying nature of the pathological response provoked (table 2).

What controls the immune response to hepatitis B virus infection is unknown. The persistence of infection acquired early in infancy has been emphasised in a number of reports. It has been suggested that infection acquired in infancy constitutes an important contribution to the pool of infective carriers particularly in a genetically susceptible population. These observations from very small series of patients must be weighed against other reports which document clearing of hepatitis B surface antigen in early infancy. Cross-sectional studies suggest that infection in early infancy does not contribute the major part in the persistence of the large infective pool in the population (Mowat, 1980; Fukeda *et al.*, 1978).

Be that as it may, there is no doubt that in areas of high incidence in the world the number of children who become infected is phenomenal. For example, in Senegal by six years of age, 80% of children have evidence of past or present infection (Maupas *et al.*, 1981). In Taiwan 15% of schoolchildren are carriers (Kang-Wen *et al.*, 1980). Not all infection is vertically acquired (table 3). While in Europe and North America hepatitis B infection is a disease affecting mainly adults, in truly international terms this is a disease of childhood – but it may have its sequelae in adult life.

Table 3. — *Sources of hepatitis B virus infection in childhood.*

Infection from mother around time of delivery
Family epidemics (transmitted via fomites, such as chewing-gum)
Papular acrodermatitis
Arthropods
Shared play-area with the possibility of skin laceration
Drug addicts
Patients on renal dialysis
Anti-haemophilic globulin

The severity of liver disease in Hepatitis B infection

What determines the severity of the pathological reaction to hepatitis B is unknown. Hepatitis B virus itself is not cytopathic. Patients who develop a good antibody response in an acute hepatitis usually clear the infection. Some of those however, do go on to develop chronic hepatitis–paradoxically, some who have had fulminant hepatic failure. Asymptomatic, smouldering or sub-clinical hepatitis may proceed to cirrhosis and hepatocellular carcinoma - even in childhood (Shimoda *et al.*, 1980). Yet others develop antibody with no other evidence of infection or hepatitis. Such a range of reactions occurs in early infancy as well as in adult life (Baumann *et al.*, 1980).

The evidence that pathological change can be related to age can therefore be challenged. There is evidence that the male sex are more liable to develop chronic liver disease (Drew *et al.*, 1978). Persistent abnormal immune reactions directed against liver membrane components induced by some genetic predisposition may also be a factor in chronic liver disease (Vergani and Eddleston, 1981). The most intriguing of recent developments is the possible role of the delta agent. Preliminary evidence suggests this is a RNA virus which can be detected only in those infected with hepatitis B virus. The delta antigen is distinct from the known hepatitis B virus antigen. It can be localised in the nuclei of liver cells of patients with chronic hepatitis B infection. Patients with delta antigen in the liver develop an antibody to the delta agent which circulates in the serum. The patterns of spread of delta infection appear. It is endemic in association with non-parenteral spread of infection in Italy, and it occurs sporadically and in association with parenteral transmission in most other geographical areas examined, for example, in the United States, Japan, Hong Kong, Taiwan, Australia and several cities in Europe. Rizzetto and co-

workers (1980) demonstrated that the delta antigen could be transmitted to susceptible chimpanzees by inoculation of serum containing surface antigen obtained from patients with delta antigen detected in the liver.

Three of the five animals inoculated developed intrahepatic delta antigen, while a fourth developed an elevation in the serum transaminase concentrations coincidental with the development of anti-delta antibody in the serum. The present data suggest that the delta antigen requires for its multiplication replication of the hepatitis B virus. Patients carrying evidence of delta particle infection are particularly prone to develop progressive liver disease.

CLINICAL FEATURES

The only clinical manifestation of hepatitis B virus infection which appears to be peculiar to childhood, is papular acrodermatitis. The identification of significant liver disease is dependent on liver biopsy in childhood as in adults.

Prevention of vertical transmission

Infants born to carrier mothers who are hepatitis Be antigen positive are very likely to become infected but contrary to what was previously believed, those born to mothers who are anti-HBe positive, may also become infected. Furthermore, such nfants are likely to be in a household where other family members are infected and may be infected from such sources (Shiraki *et al.*, 1980).

There are two possible means of detecting such infants. Uncontrolled observations have indicated that the administration of gammaglobulin containing high concentrations of antibody to hepatitis B (hyperimmune gammaglobulin) if given within 48 hrs of delivery and repeated at monthly intervals up to six months, is protective during this period (Reesink *et al.*, 1979). Preliminary reports of a controlled study are also encouraging (Stevens *et al.*, 1981). Such passive immunity can only be temporary. The early reports of active immunization (Maupas *et al.*, 1981) are very encouraging. The development of inexpensive, safe vaccines, perhaps based on a chemically well identified polypeptide sub-unit of the hepatitis B virus, could clearly make an immense impact on this world-wide disease (Zuckerman, 1980).

Non-A, non-B Hepatitis

Data on this condition in children are still scanty. Acute non-A, non-B hepatitis in the last trimester of pregnancy has been associated with transient elevation of the transaminases in five infants (Tong *et al.*, 1978). 11 of 199 children hospitalized because of acute hepatitis in West Germany were considered to have non-A, non-B hepatitis (Franzen *et al.*, 1979). Only 2 of 48 cases of non-A, non-B hepatitis identified in West London occurred in children of less than 15 years of age (Farrow *et al.*, 1981).

REFERENCES

Balistreri W. F., Suchy F. J., Farrell M. K., Hubei J. E.: Journal of Paediatrics, *98*, 399, 1981.
Bangura B., Morecki R., Glaser J. H., Gartner L. M., Horwitz M. S.: Laboratory Investigation, *43*, 456, 1980.
Baumann, Arnold W., Meyer zum Büschenfelde K. H.: Monatsschrift Kinderheilkd, *128*, 518, 1980.
Dienstag J. L.: *Viral hepatitis Type A: Virology and Course.* In: "Clinics in Gastroenterology", vol. 9, No. 1, S. Sherlock (ed.), p. 135, Saunders, Philadelphia, 1980.
Drew J. S., London W. T., Lustbader E. D., Hesser J. E., Blumberg B. S.: Science, *20*, 687, 1978.
Farrow L. J., Stewart J. S., Stern H., Clifford R. E., Smith H. G., Zuckerman A. J.: Lancet, *1*, 982, 1981.
Franzen C., Brodersen M., Frisner G.: European Journal of Paediatrics, *132*, 261, 1979.
Frommel D., Good R. A.: *Immunological mechanisms.* In: "Recent Advances in Paediatrics", 4th edition, D. Gairdner and D. Hull (eds.), p. 401, J. A. Churchill, London, 1971.
Fukuda N., Nojima M., Adachi N.: Acta Hepatologica Japonica, *19*, 936, 1978.
Hopper R., Jueles C. W., Routenberg J. A., Harrison W. O., Kilpatrick M. E., Kendra S. J., Dienstag J. L.: American Journal of Epidemiology, *105*, 148, 1977.
Jenkins B. J., Williams R.: *Fulminant viral hepatitis.* In: "Clinics in Gasroenterology", vol. 9, No. 1, S. Sherlock (ed.), p. 171, Saunders, London, 1980.
Kang-Wen W., Liuchang S., Chung-Hsing L., Tang-Hsien W.: Chinese Journal of Paediatric Medicine, *2*, 87, 1980.
Maisels M. J.: *Neonatal Jaundice.* In: "Neonatology, Physiology and Management of the Newborn", IInd edition, B. G. Avery (ed.), p. 473, J. B. Winnacott Co., Philadelphia, 1981.
Maupas P., Chiron J. P., Barin F.: Lancet, *1*, 289, 1981.
Mowat A. P.: *Infections associated with Hepatitis in Infancy.* In: "Liver Disorders in Childhood", p. 59, Butterworths, London, 1979.
Mowat A. P.: *Viral Hepatitis in Infancy and Childhood.* In: "Clinics in Gastroenterology", vol. 9, No. 1, p. 191, S. Sherlock (ed.), Saunders, London, 1980.
Portmann B., Mowat A. P., Williams R.: Acta Paediatrica Belgica, *29*, 139, 1976.
Rakela J., Mosley W. J.: Journal of Infectious Diseases, *135*, 933, 1977.
Reesink H. W., Reesink-Brongers E. E., Lafeber-Schut B. J.: Lancet, *2*, 436, 1979.
Rizzetto M., Hoyer B., Canese M. G., Shih J. W., Purcell R. H., Gerin A. L.: *Delta agent. Association of delta agent with Hepatitis B surface antigen and RNA in serum of delta infected chimpanzees.* Proceedings of the National Academy of Science of the United States of America, *77*, 6124, 1980.
Shimoda T., Uchida T., Miyata H.: American Journal of Clinical Pathology, *74*, 827, 1980.

Shiraki K., Yoshihara M., Sakurai M., Eto T., Kawana T.: Journal of Paediatrics, *97*, 768, 1980.

Skinhoj P., Mickelsen F., Hollinger F. B.: American Journal of Epidemiology, *105*, 140, 1977.

Stakhanova V. M., Vyazoy S. O., Doroshenko N. V.: Lancet, *2*, 631, 1979.

Stevens R., Beasley R. P., Szmuness W.: *Efficacy of Hepatitis B immunoglobulin in prevention of perinatally transmitted Hepatitis B.* Presented at The International Symposium on Viral Hepatitis, New York, April 1981.

Tong M. J., Rakela J., McPeak C. A. M.: Gastroenterology, *75*, 991, 1978.

Vergani G. M., Eddleston A. L. W. F.: *Auto-immunity to liver membrane antigens in acute and chronic hepatitis.* In: "Clinics in Immunology and Allergy", vol. 1, No. 1, p. 181, Saunders & Co., London, 1981.

Wong D., Purcel R. H., Sreenivasan M. A.: Lancet, *2*, 876, 1980.

Zuckerman A. J.: *Prophylaxis of Hepatitis type B: Immunoglobulin vaccine.* In: "Clinics in Gastroenterology", vol. 9 (1). S. Sherlock (ed.), Saunders, London, 1980, p. 65.