Viral hepatitis

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In the last few years important research developments have clarified the molecular biology, diagnosis, epidemiology, and clinical features of five distinct hepatotropic viruses, that is A, B, C, D, and E. Vaccines giving active protective immunity are now available for hepatitis A and B infection, the most frequently identified causes of hepatitis in children. The emergence of hepatitis B mutants in some patients with a good antibody response to the present vaccines is a cause for concern. Prolonged treatment with parenteral interferon reduces the rate of replication of hepatitis B and C, enhances the immune response, and improves the liver function tests in a proportion of chronically infected children. This review summarises clinically significant developments in paediatric aspects of these five forms of viral hepatitis.

Typical cases of type A and E hepatitis are characterised during the _preicteric phase_ by non-specific symptoms of anorexia, nausea/vomiting, lassitude, fever, and sometimes intermittent dull abdominal pain in the epigastrium or right hypochondrium. There may be tender hepatomegaly, splenomegaly, and lymph node enlargement. These symptoms often regress during the _icteric phase_ when bilirubinuria, pale/clay coloured stools, and jaundice appear. In older children, as in adults, a recurrence of the original symptoms may occur with type A hepatitis, with in some cases, pruritus and depression, and jaundice persisting for a variable period. In anicteric hepatitis B, C, and D systemic symptoms are less frequent. A firm or hard non-tender hepatomegaly, splenomegaly, and cutaneous features of spider naevi, cutaneous shunt, or palmar erythema suggest chronic liver disease. In all forms of acute hepatitis, the serum transaminase levels are raised, whereas these may be normal in those with chronic disease. A prolonged prothrombin time should raise suspicion of severe hepatic necrosis or decompensation of an underlying liver disease.

**Hepatitis A virus**

The hepatitis A virus is a 27 nm unenveloped, symmetrical RNA virus belonging to the picorna group of viruses. Although minor genetic differences are found in isolates of the virus, these do not appear to affect its pathogenicity or the immune response to infection. Diagnosis of acute infection is made by detection of IgM antibodies. The distribution of the disease is worldwide and transmission is almost exclusively by the faecal-oral route. In developing countries with poor living conditions like Liberia, up to 70% are seropositive to hepatitis A virus at 4 years of age. In Thailand and Hong Kong the IgG antibody prevalence among children 10 to 15 years old has fallen by threefold in the last decade to 15–25% in 1991 presumably due to economic growth and improved levels of public sanitation and education.

In the UK, only 8% of 102 medical students (age 19–31) have serological evidence of past hepatitis A virus infection. Unexpectedly high antihepatitis A virus prevalence rates were found in a recent community wide epidemic in a UK city at 27%, 38%, and 22% in 1–4, 5–7, and 8–10 year old children respectively. Thus although with improved living standards hepatitis A may become largely a disease of adult life, children are still at risk if hygienic standards are not maintained. This study also emphasised that the proportion of infected children developing icteric hepatitis increases with age: only one of 43 children less than 5 years became icteric as compared with one in 4·7 of those 8–10 years old. Infection in pregnancy has no apparent effect on the fetus or newborn. Neonates even when infected parenterally by blood transfusion from a donor in the prodromal phase of the disease rarely show even biochemical evidence of hepatitis. They are a potential source of infection of symptomatic icteric hepatitis in non-immune staff as the virus is excreted in the stools for up to five months. This is longer than has been demonstrated in older children except when icteric hepatitis relapses, as has been reported in 3–20% of children. After icteric hepatitis in children, the liver function tests may remain abnormal for a long time; 25% were abnormal after six months in one study. Neither a chronic carrier state nor chronic liver disease has been observed.

Altogether 99–99% of children ultimately recover completely. For the very rare patient (0·1%) with acute liver failure as evidenced by hepatic encephalopathy and impaired clotting, there is a 30% death rate without liver transplantation. If the international normalised prothrombin ratio (INR) is greater than 1·6, it is essential to consider transfer to a unit able to perform liver transplantation. The degree of prolongation of the prothrombin time, after parenteral vitamin K, is a better early indicator of prognosis rather than the initial severity of encephalopathy. The INR...
may rapidly increase to >4 at which level the patient should be listed for transplantation before irreversible cerebral oedema occurs.15

PREVENTION
Active immunisation against hepatitis A virus infection using formalin inactivated attenuated virus strains is effective in children and should replace passive immunisation which only protects for three to six months.3 Vaccine efficacy in children has been demonstrated in two studies.16,17 In 38,000 Thai schoolchildren (age 2–16 years) either hepatitis A virus or hepatitis B virus vaccine was given at 0, 1, and 12 months in the first or in the second 18 months of a three year study. Hepatitis A virus vaccine protected 97% of recipients against infection one month after administration of two doses, and antibodies persisted for at least a year.16 In a placebo controlled study of 1037 Jewish children, a single dose of vaccine, equivalent to 25 units of hepatitis A virus antigen prevented infection after 21 days. Only one of 305 recipients had undetectable antibodies one month after vaccination. Before day 21 three cases occurred in the placebo group and seven in the vaccine group. Thirty 6–10 further cases occurred in those receiving placebo.17

Currently booster doses are recommended at 6–18 months but the duration of protection is not known; it could be life long. Whether active and passive immunisation at a different site would give earlier protection is unknown. The vaccine is not yet licenced for use in children in the UK. Active immunisation will benefit many groups such as child care or health care workers and travellers to endemic areas. Vaccination of school entrants and leavers as a temporary measure and universal childhood vaccination currently established immunisation programmes should prove the most cost effective method of protection.

Hepatitis B virus
The hepatitis B virus is a hepaDNA virus, with four distinct genomic regions and a complex mode of replication that may predispose to the development of mutant forms.18 Diagnosis is made by the detection of hepatitis B surface antigen (HBsAg) in the peripheral blood with hepatitis B virus DNA indicating active replication. If associated with hepatitis Be antigen (HBeAg) the patient carries a larger virus load and is more infective. Acute and ongoing chronic infection is associated with antihepatitis Bc IgM. Antihepatitis Be (anti-HBe) and later antihepatitis B surface (anti-HBs) antibodies appear as an effective immune response develops. The delayed or absent immune response in the chronic carrier is unexplained. Even those with anti-HBs may have viral DNA in blood and/or liver tissue when tested using polymerase chain reaction techniques. Transmission, percutaneous, percutaneous or transmucosal, is either in blood or contaminated body fluids from acutely infected patients or carriers.

Acute and chronic hepatitis B infection is primarily a disease acquired in childhood in Africa19,20 and China21 where 15–20% of the population are HBsAg carriers. The hepatitis B virus infection is established at birth in 2–5% of infants born to infected mothers, indicating in utero infection.22 Infection occurs in 40% in early infancy in Taiwan23 but in only 1–5% in sub-Saharan Africa.19,20 The difference is in part explained by the higher prevalence of HBeAg in Chinese (40%) than African (15%) mothers. In Africa the majority of infections are acquired between 6 months and 6 years of age with other family members implicated as a source of infection (horizontal transmission).19 In areas of intermediate endemicity (2–8%: Italy, Japan, Spain, Greece, and Portugal), infection occurs in both children and adults.24 In areas of low endemicity (<1%: north west Europe, North America, UK, and Australia), infection in infancy and childhood is uncommon.

In general the younger the age at infection, the less the frequency of symptomatic disease, but the greater the risk of a failure of antibody response and hence, of carrying the virus for many years. More than 90% of infants infected during the first year of life become chronic carriers compared with 6–10% if infection occurs after the sixth year of life.25 A degree of immune tolerance is established. Such chronicity increases the chances of cirrhosis and hepatocellular carcinoma25 but the risks are at present difficult to quantify. Males have a higher risk of developing histologically aggressive disease with progression to cirrhosis.25–27 Coinfection or superinfection with delta hepatitis (see below) increases the risk of progressive disease.

CLINICAL FEATURES
The majority of infected infants have no symptoms at the time of infection and become asymptomatic 'healthy' chronic carriers of the virus. Symptomatic cases usually present as an acute hepatitis indistinguishable from a type A hepatitis or with complications of cirrhosis or with hepatocellular carcinoma. Less than 10% presenting with acute disease become chronic carriers.13 Acute liver failure which occurs in <1% may be associated with an unusually intense antibody response. Coinfection or superinfection with delta hepatitis may be responsible. Fulminant hepatitis secondary to perinatal hepatitis B virus infection has been reported in infants from 2–6 months of life.28,29 particularly if the mother is anti-HBe positive29 (prevention: see below). Mutations in the precore region of the hepatitis B virus DNA may have contributed to pathogenesis of fulminant hepatitis B in this age group.30 Another worrying find is mutation in the virus DNA which alters the components of the surface antigen to evade antibodies to the normal virus.31 Death may occur in 60% of patients with fulminant hepatitis B, unless they are transplanted. Hepatitis B virus infection of the graft is unusual in contrast to the patient receiving a transplant for chronic hepatitis B virus disease.
CHRONIC HEPATITIS

The risks associated with chronicity and the rate of progression are difficult to quantify. The absence of clinical and biochemical features of liver damage does not exclude severe pathological changes. In studies of almost 350 children followed up from one to 10 years no progression of liver disease was noted, although almost 50% had histological findings of chronic active hepatitis or cirrhosis at presentation.21,27 In childhood hepatitis B virus infection may rarely be associated with hepatocellular carcinoma25,32 even in the absence of cirrhosis but what contributes to the development of neoplasia in children as adults is unclear. In Taiwan 51 consecutive children with hepatocellular carcinoma had detectable HBsAg, either in the blood or in the liver tissue.25 In West Germany, seven of 11 (64%) cases of hepatocellular carcinoma in childhood had positive HBsAg serology.32 Integration hepatitis B virus DNA sequence have been found in neoplastic liver tissues of children without other serological evidence of hepatitis B virus infection.

PREVENTION

Three strategies for prevention of hepatitis B virus infection have been reported.33,34 (1) In areas in which most hepatitis B virus infection is acquired perinatally, the administration of hepatitis B immunoglobulin and hepatitis B vaccine to all infants within 24 hours of birth has been shown to be effective in up to 95% of infants. (2) In areas such as Africa and Italy where the majority of infections occur after five months of life, combining hepatitis B virus vaccination into the routine childhood immunisation programme in the first four months of life is equally effective. This scheme is particularly attractive to countries unable to afford hepatitis B immunoglobulin. (3) In areas of low endemicity, for example the UK, the most economic approach is the screening of all pregnant women for HBsAg and immunisation of the newborns of all HBsAg positive mothers, whether HBeAg positive or not, with specific immunoglobulin and vaccine. The duration of protection is not known. Booster doses are currently given after three to five years to maintain an antibody titre greater than 100 mIU/ml, which is certainly protective, unless viral mutation occurs.31 The emergence of viral mutants may jeopardise current plans to limit hepatitis B virus infection, and should stimulate the production of more effective vaccines.

TREATMENT

In treating chronic hepatitis B infection, the ultimate goals are to eradicate the virus and ameliorate the underlying liver disease. The only agent for which some efficacy has been demonstrated in controlled studies is interferon alfa (IFN-α). IFN-α which inhibits viral entry into host cells and the rate of viral replication and enhances cellular and antibody dependent immunity has increased the rate of clearance of HBeAg (which reflects the rate of viral replication) and seroconversion to anti-HBe in controlled studies. Rates of spontaneous seroconversion, which was higher when there was biochemical and histological evidence of active hepatitis, were increased by two to threefold with doses ranging from 3 MU/m² three times a week for 26 weeks to 10 MU/m² given similarly for six or nine months.35-37 Prior prednisolone treatment did not improve efficacy.38 Note that in these studies very few children developed anti-HBs. Further extensive controlled studies are needed using different doses and duration of interferon with patients stratified for sex, intensity of viral replication, and disease activity.

HEPATITIS C VIRUS

The hepatitis C virus has not yet been visualised but molecular biological techniques indicated that it is a 30 to 60 nm enveloped, single stranded heterogenous RNA virus, distantly related to the flaviviruses and pestiviruses.39,40 The RNA genome is composed of 10,000 nucleotides which is bound to a nucleocapsid and covered by a glycoprotein coat. At least six genetic types have been identified to date but it is as yet unclear whether these have particular pathogenic or therapeutic significance.

DIAGNOSIS

At present, diagnosis of hepatitis C virus infection is usually made by detection of antibody to components of the virus or by polymerase chain reaction techniques that detect a part of the hepatitis C virus genome. The latter are available on a research basis only. The first generation assay, using an enzyme linked immunoassay (ELISA) technique was based on demonstration of antibody to a single non-structural protein. This test has been found to have a low sensitivity and antibody only became evident four to 52 weeks after onset of infection. False positive reactivity may also occur in patients with rheumatoid factor, hypergamma-globulinaemia (particularly in patients with autoimmune hepatitis), and in those with para-proteinemia. Subsequent assays testing for additional virus components have increased specificity and sensitivity, detecting antibodies as early as two weeks and always within 20 weeks from onset of infection. It remains unclear however whether a positive antihepatitis C virus indicates an active disease or only implies a past infection. Recently, on-going viral replication has been inferred by detection of hepatitis C virus RNA sequences in liver and serum, using the polymerase chain reaction assay. This method, although highly sensitive, requires adequate selection of diagnostic primers, present in different hepatitis C virus variants, but not in other viruses, to ensure a high specificity. RNA assays, which are currently beyond the capabilities of most clinical laboratories, are usually positive in patients in whom antibodies are detected but can give positive results in patients without antibodies.
It is too early to assess the clinical or pathological significance of the various antibodies to components of hepatitis C virus or hepatitis C virus RNA positivity. The clinician who suspects hepatitis C virus infection should ask the laboratory to test for antibodies to hepatitis C virus, using a second generation assay. If the patient has had transfusion of blood products, and other causes of liver disease have been excluded, hepatitis C virus RNA should be tested by the polymerase chain reaction.

PREVALENCE
The epidemiological and clinical features of hepatitis C virus infection in children given below used first generation assays. A study of 696 children (aged 4–14 years) in Cameroon demonstrated at 14-5% seroprevalence for antihepatitis C virus, which increased steadily with age from 6-6% in 4–6 years old to 17-5% for those aged 11–14 years. In 4496 Saudi Arabian children (1–10 years), a prevalence rate of 0-9% was reported. Screening of high risk groups have shown a 95% antihepatitis C virus seropositivity in 22 children with haemophilia (age 2–5–11 years) who were regularly transfused with dry heat treated factor VIII concentrates. Of 50 children with leukaemia who were in long term remission, 12 (24%) were persistently positive for antihepatitis C virus. In children with chronic cryp-
genic hepatitis, hepatitis C virus antibodies were found in 16 of 33 (48%) in Italy and in 14 of 144 (9-7%) in Taiwan. In dialysed patients, the five of 27 (18%) who were antihepatitis C virus positive had received haemodialysis for a mean of 105 months as opposed to 41 months in the antihepatitis C virus negative patients.

TRANSMISSION
It is believed that hepatitis C virus is transmitted by parenteral exposure and accounts for 95% of post-transfusion hepatitis. Vertical transmission, that is infection from the mother but not necessarily in utero is very rare but can occur usually in the second year of life in up to 20% if the mother has HIV infection. In about a third of patients there is no known source of infection. The incubation period after blood transfusion is usually seven to eight weeks with a range from two to 26 weeks. A shorter incubation period has been noted after administration of infected coagulation factors.

CLINICAL FEATURES
In both children and adults, hepatitis C virus can cause an acute hepatitis that is indistinguishable from other forms of acute viral hepatitis except that the serum transaminase may fluctuate up to 15-fold and fulminating disease has not been recognised. Chronicity is believed to occur in 30 to 70%. In children the majority of reported cases have had chronic disease. In 16 Italian children with chronic cryptogenic hepatitis, 11 were asymptomatic at presentation and five had mild non-specific symptoms (abdominal pain, anorexia, and asthenia). Hepatomegaly was noted in six patients and splenomegaly in three. The mean alanine transaminase level at presentation was 167 (108) IU/l. Some of the children had normal aspartate aminotransferase levels. Nine patients had a liver biopsy that showed chronic lobular/persistent hepatitis in five, chronic active hepatitis in three, and cirrhosis in one. Over a follow up period from one to 14 years (mean 5-3 (2-9) years), no child developed liver failure but only one of 11 antihepatitis C virus positive patients normalised their alanine transaminase. Of 50 children with leukaemia in long term remission who were observed from one to 13 years, 12 (24%) persistently antihepatitis C virus positive patients with persistently raised transaminase had more severe histological lesions than those who were transiently positive or negative for antihepatitis C virus, using the second generation recombinant immunoblot assay. For this group of patients therefore, antibodies to hepatitis C virus appear as markers of ongoing infection and may be used to predict the severity and course of chronic liver disease.

There is an interesting link between hepatitis C virus infection and liver kidney microsomal type 1 (LKM-1) antibody, a serological marker for autoimmune hepatitis. The prevalence of past or present hepatitis C virus infection in LKM-1 antibody positive varies from 0 to 88% in different geographical areas. The prevalence of LKM-1 positivity in populations positive for hepatitis C virus infection is 0 to 5%. Hepatitis C virus infection may be followed by an IgM and then an IgG LKM-1 response. Present evidence suggests that there are differences in the target antigens of LKM positive patients, with or without evidence of hepatitis C virus infection which implies that they represent two distinct groups. Clarification of the association is essential as classical autoimmune hepatitis is treated with immunosuppression, which could exacerbate viral infection, while antiviral agents such as interferon used to treat hepatitis C virus infection may worsen autoimmune disease.

PREVENTION AND TREATMENT
Screening of blood donors for antihepatitis C virus and use of vapour heat and wet heat treated clotting factor concentrates will decrease the risk of hepatitis C virus transmission.

Prolonged treatment with IFN-α (for example 3–5 MU/m² three times a week for 48–60 weeks) has been shown in uncontrolled studies with small number of children to normalise transaminase levels in 30–50% with disappearance of hepatitis C virus RNA from the serum in some patients (S de Virgilis et al and R Iorio et al, work presented at the second joint meeting of the British and Italian societies of Paediatric Gastroenterology and Nutrition, Cambridge 1992).
Hepatitis D virus (delta agent)
The hepatitis D virus is a defective 36 nm single stranded circular RNA virus which requires the hepatitis B surface antigen for its assembly and virulence.\(^5\)\(^7\) It is transmitted in a similar fashion to hepatitis B virus. Infection may occur at the same time or subsequent to earlier hepatitis B infection. The severity of liver damage is markedly increased if there is active hepatitis B virus replication. Diagnosis is established by detecting IgM antibodies in acute infection and IgG in chronic infection. The delta antigen is present in the serum in acute infection. There is considerable regional variation in its prevalence. Infection rates in hepatitis D virus infected children range from 1-6% in Taiwan, 12-5% in parts of Italy, China and the Balkans, and up to 25% in the Amazon basin in Brazil.\(^5\)\(^8\)\(^-\)\(^6\)

CLINICAL FEATURES
Perinatal infection has been described in an infant born to an HBeAg/antihepatitis D virus positive mother but in none of those whose mother was anti-HBe positive.\(^6\) Coinfection with hepatitis B virus causes a biphasic rise in transaminases, the second due to hepatitis B virus. It is often asymptomatic with complete recovery but may be fulminant in 2-7%, with the majority of cases occurring in males and in children less than 15 years of age. Superinfection causes exacerbation of liver disease producing acute or fulminant hepatitis or a more severe chronic hepatitis which rapidly leads to liver failure compared with hepatitis B virus infection alone but a small percentage eventually achieve remission.

PREVENTION AND TREATMENT
Infection may be prevented by giving only antihepatitis D virus negative blood or blood products to HBsAg positive patients. Hepatitis B virus vaccination will prevent hepatitis D virus infection and should limit its spread. There is no specific treatment for hepatitis D virus infection. Curiously after transplantation for chronic liver disease, hepatitis D virus may reinfect the graft without hepatitis B virus infection.\(^6\)

Hepatitis E virus
The hepatitis E virus is a 27 to 30 nm nonenveloped, single stranded RNA virus which shares the biophysical and biochemical features of calciviruses.\(^6\) It is the causative agent of what was described on epidemiological grounds as enterically transmitted, epidemic or faecal-oral non-A, non-B hepatitis. Apparently waterborne epidemics occurred in the Indian subcontinent, Southeast and Central Asia, Africa, and North America. Specific diagnosis by polymerase chain reaction techniques for genomic sequences or by antibody detection is now available but only a few studies have been reported.\(^5\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\) Sporadic cases have been reported in West Africa and in developed countries like the UK in those visiting endemic areas. The incubation period is six weeks (range 2-9 weeks). There is a low secondary attack rate among exposed household members. Icteric cases were rarely recognised in children in epidemics but of 39 Sudanese children with acute hepatitis, 23 (mean age 7:2 (3-1) years, range 2-13; 16 males) were found to be IgM positive, using a western blot assay. Three of 39 control children also had antibody.\(^6\)

CONCLUSIONS
A precise serological identification of the causative virus is essential in the management of acute or chronic hepatitis. If negative, the child may require specific treatment for acute (for example Salmonella typhi) or chronic disease (for example Wilson’s disease, autoimmune hepatitis) or surgery including liver transplantation. Although non-A, non-B, non-C, non-E viral hepatitis may occur, it is not a diagnosis! Hepatitis A is likely to emerge as a health hazard as improvement in hygiene delays the age at infection and thus the risk of asymptomatic disease. Universal vaccination against hepatitis A should be considered in developed countries. Strategies for hepatitis B immunisation should be related to the local epidemiological observations. The emergence of hepatitis B virus mutants is a potential danger which could be minimised by the development of vaccine against other viral components. More studies are required to define the importance of hepatitis E and C in childhood, particularly the role of C in causing autoimmune hepatitis. Further controlled trials are needed to determine which patients with chronic hepatitis B and C should be treated with interferon and the optimum dose and duration of treatment.

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