Viral hepatitis B and C in children

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Viral hepatitis B and C are the cause of significant disease worldwide. Acute infection is more common with hepatitis B than C in childhood; but chronic asymptomatic infection leading to chronic liver disease and hepatocellular carcinoma is a considerable concern.

The natural history of hepatitis B is well established in adults but the long-term outcome for children is still under debate. Following an acute infection, 90% will recover spontaneously; but approximately 1% of patients develop acute fulminant hepatitis requiring liver transplantation. The main source of infection in childhood is perinatal transmission, which is effectively prevented using vaccination, antenatal screening and screening of blood products and organ donors. The vaccine is effective in 97% of newborn infants and lasts for 10–15 years.

All children with chronic hepatitis B infection should be annually monitored and those with persistent infection should be considered for anti-viral therapy. Treatment options include Interferon (5 M units per m² subcutaneously $\times$ 3 weekly for 6 months) or Lamivudine (3 mg/kg for 12–24 months), but neither therapy is completely effective. Interferon clears viral infection in 20%–40% and is most effective in children with elevated transaminases or horizontal transmission. Only 23% seroconvert after lamivudine, 26% of whom may develop resistance with YMDD mutant variants of the hepatitis B virus. A number of other drugs, such as Adefovir Dipivoxil, Famciclovir, Entecavir and Pegylated Interferon, are under evaluation. Liver transplantation is an effective treatment for children with acute or chronic liver failure, but recurrence is high without prophylaxis.

The main route of transmission for hepatitis C was originally through infected blood products or organs; but now the most common source is vertical transmission which ranges from 2%–12% depending on maternal infectivity. Breast feeding is safe in mothers with low titres of hepatitis C RNA.

The natural spontaneous clearance rate for hepatitis C is between 20% and 40% and is higher in children who have been parenterally infected compared to perinatal infection. It is a mild disease in children, but the indication for

treatment is based on the future risk of cirrhosis and hepatocellular cancer.

Children with persistent infection (hepatitis C RNA positive for 6 months) and evidence of histological disease should be considered for combination treatment with Pegylated Interferon (3 M units/m² subcutaneously $\times$ 1 weekly) and oral Ribavirin (15 mg/kg) which has a sustained response rate of 80%–100% for genotypes 2 and 3, and 50% for genotype 1. Liver transplantation for hepatitis C in children is rarely required, but 100% recurrence can be expected without prophylaxis.

Emerging new therapies include viral enzyme inhibitors, cytokines, antisense oligonucleosides which are at an early stage of development.

INTRODUCTION

Infection with viral hepatitis B and C leads to significant disease in children on a worldwide basis. Acute symptomatic hepatitis is rare in childhood, but chronic asymptomatic infection (i.e. virus persisting for at least 6 months) carries a risk of chronic liver disease and hepatocellular carcinoma is a major concern.^{1,2}

Children with persistent viral hepatitis B or C should be seen annually in order to:

- detect natural seroconversion
- development of chronic liver disease or hepatocellular carcinoma (Box 1)
- and to consider antiviral therapy.

It is essential that the children are encouraged to lead a normal life and are not stigmatized by their disease—this requires sensitivity from schools and nurseries.

METHODS

This review is based on my personal experience and the experience of both the paediatric and adult Liver Units at Birmingham Children's Hospital and the Queen Elizabeth Hospital, Birmingham. It is supported by reviewing the relevant literature through a Medline search.

HEPATITIS B

The diagnosis of hepatitis B is made by detecting hepatitis B surface antigens (HBsAg) at any time. Acute infection is

Box 1 Monitoring hepatitis B and C carriers**Annual review**

Check for

- 1 Seroconversion
HBsAg / HBeAg/hepatitis B-DNA
Hepatitis C antibodies / hepatitis C-RNA
- 2 Progression of liver disease
- 3 Development of hepatocellular cancer
Abdominal ultrasound
 α fetoprotein
- 4 Consider anti-viral therapy
Hepatitis B: Lamivudine/Adefovir
Hepatitis C: Pegylated Interferon/Ribavirin

detected by IgM anticore antibodies to hepatitis B while chronic hepatitis is demonstrated by the presence of IgG anticore antibodies to hepatitis B. Hepatitis Be antigen (HBeAg) may be present in acute or chronic infection, but persistent HBeAg after 6 months suggests a high level of chronic infection. Quantitative assay of hepatitis B DNA indicates the level of viral load and determines infectivity.

The natural history of hepatitis B is well established in adults but the long-term outcome for children and the role of therapy is unclear.

Following an acute infection, 90% of older (>3months) children will recover spontaneously, but less than 1% of patients develop acute fulminant hepatitis requiring liver transplantation.³ Neonates, who are infected by perinatal transmission usually become chronically infected and chronic carriers.

The main source of infection worldwide is perinatal transmission. Mothers who are HBe antigen positive have the highest infectivity and a 70%–90% risk of transmitting infection to their infant. Mothers who are HBe antibody positive have a low risk of transmitting infection, but there is a risk of the babies developing fulminant hepatitis, possibly due to a mutant virus⁴ unless vaccinated.

The transmission of hepatitis B is effectively prevented using vaccination and health education strategies. These include screening blood products and organ donors and antenatal screening, which is now mandatory in the UK. Recombinant hepatitis vaccine is effective in 97% of new born infants and it is essential to immunize all at-risk infants, which requires close collaboration between obstetricians, paediatricians and general practitioners. Alternative vaccination strategies, suggested by the World Health Organization, include universal immunization of all

infants either at birth, in high endemicity areas, or as part of the national immunization programme, in infants or adolescents in low endemicity populations.⁵

Vaccination schedules for the neonate are mandatory for those born to hepatitis B positive mothers. The schedules include immunization at birth with hepatitis B immunoglobulin (only if the mother is HBeAg positive) and three or four injections of vaccine over 6 months for all infants; older children and adults should receive three doses of the hepatitis B vaccine over 6 months. Recent studies have indicated that immunological response lasts for at least 10 years, suggesting that a booster dose may be required for at risk populations.^{6,7}

The efficacy of hepatitis B vaccination has been demonstrated in Taiwan where the hepatitis B carriage rate at 16 years has fallen from 10.6% in 1983 to 0.8% 1993 following the introduction of universal vaccination. There has also been a reduction in the annual incidence of hepatocellular carcinoma in children from 0.7–0.36/100 000 over this time period.⁸

Natural history of hepatitis B

The natural history of chronic hepatitis B infection in childhood varies with the route of infection. The rate of seroconversion is lower in perinatally infected infants⁹ than in horizontally infected infants,¹⁰ and is thought to be higher in girls than in boys. Children are usually asymptomatic without signs of chronic liver disease. Biochemical parameters indicate mild elevation of hepatic transaminases (80–150 μ /L) with normal albumin, coagulation, and alkaline phosphatase. Liver histology indicates a chronic hepatitis in over 90% of the carriers, which may be mild or nonspecific in 40% of children. There is little correlation between transaminase elevation and the extent of hepatitis.⁹ Progression to cirrhosis and to hepatocellular carcinoma in childhood has been documented.^{8,11}

Management of chronic hepatitis B infection

Currently, most chronic hepatitis B carrier children are either new migrants or vaccine failures. They should be referred to a specialist paediatric centre so that the family may be supported and counselled, screened and immunized. Annual review should include hepatitis B serology and viral markers of hepatitis B DNA, standard liver function tests, α -fetoprotein, and abdominal ultrasound to detect evidence of seroconversion, progressive liver disease and/or hepatocellular carcinoma and considered for anti-viral therapy. The indications for treatment are:

- persistent infection HBe antigen positive >6 months
- evidence of hepatic inflammation either by elevated aminotransferase enzymes or by liver biopsy.

Treatment options include Interferon, Lamivudine and Adefovir Dipivoxil.

Interferon

Interferon is a naturally occurring protein, which enhances the immune response by stimulating lymphocyte proliferation, increasing major histocompatibility complex antigen expression and increasing natural killer cell activity. It degrades viral mRNA and inhibits viral protein synthesis. The European consensus on Interferon therapy suggests pre and post therapy liver biopsy, Interferon 5 M units per m² subcutaneously $\times 3$ weekly for 6 months.¹² In the short term, the efficacy of Interferon treatment ranges from 20%–40% and is highest in children with elevated transaminases and those who have been infected by horizontal transmission.¹³ The role of prednisolone priming is unproven but it is possible that it increases the spontaneous remission rate and reduces time to seroconversion.¹⁴

Lamivudine

Lamivudine is a pyrimidine nucleoside analogue which prevents replication of hepatitis B in infected hepatocytes. It is incorporated into viral DNA leading to chain termination and competitively inhibits viral reverse transcriptase. It leads to a rapid reduction in plasma hepatitis B DNA in most patients within 2 weeks of commencing treatment. Response rates are related to low pretreatment hepatitis B DNA levels and evidence of hepatic inflammation as detected by raised aminotransferase enzymes. In children, a double blind placebo controlled trial of 286 children with chronic hepatitis B, showed a complete response, that is, HBe antigen clearance or undetectable hepatitis B DNA after 52 weeks in 23% of children compared to 13% in the placebo group.¹⁵ Although longer-term treatment increases seroconversion rates, the main limitation of Lamivudine treatment is the high relapse rate following cessation of therapy and the development of resistance with the development of YMDD mutant variants of hepatitis B.¹⁶

Adefovir Dipivoxil

Adefovir Dipivoxil is a purine analogue, which inhibits DNA polymerase. Adult studies indicate a relatively low seroconversion rate similar to Lamivudine but it is effective against YMDD mutants and is well tolerated.^{17,18} A paediatric pharmacokinetic study has established the dosage in children and a multicentre treatment trial is under way.

Liver Transplantation

Liver transplantation is effective treatment for children with acute or chronic liver failure. The recurrence of hepatitis B is unusual following transplantation for acute fulminant hepatitis but is invariable following transplantation for

chronic hepatitis B unless prevented with a combination of oral Lamivudine and hepatitis B immune globulin.^{19,20}

Future therapy for hepatitis B in children

A number of other nucleoside/nucleotide analogues are under evaluation, such as Famciclovir, which is a guanosine analogue, and Entecavir, which is a deoxyguanosine analogue. Neither has been evaluated in children. Early results with the combination of pegylated Interferon (a long-acting interferon which only needs to be given once a week) and lamivudine has encouraging results in adults,²¹ but no trials are planned in children as yet.

HEPATITIS C

Hepatitis C is a flavivirus which was cloned in 1989.²² It is an RNA virus with a high degree of heterogeneity leading to the rapid accumulation of mutations. This genetic diversity allows the virus to avoid immune surveillance leading to chronic infection and difficulty in producing an effective vaccine.²³ There are six major genotypes with different subtypes and a distinct geographical distribution. Diagnostic assays for hepatitis C are now well established. The most useful screening test is the detection of anti-hepatitis C IgG in serum using an enzyme immunoassay (EIA) but the detection of hepatitis C RNA is necessary to determine infectivity and response to therapy.

Initially, the main route of transmission for hepatitis C was parenterally from blood products or transplanted organs. However, now the main source of infection is from intravenous drug abusers or children offered for adoption from abroad. Intrafamilial spread is uncommon, but the main source of infection in children in the UK is perinatal transmission from infected mothers.^{24,25} Transmission of infection is higher in mothers with high titres of hepatitis C RNA and with those who are HIV positive^{26,27} with transmission rates varying from 2%–12% depending on maternal infectivity. Hepatitis C antibody is passively transmitted, and so all infants will have the antibody for up to 13 months.²⁸ Measurement of hepatitis C RNA, which may be positive between 1 and 3 months of age, is necessary to detect active infection.²⁸ Breast feeding is safe in mothers with low titres of hepatitis C RNA.²⁹

There is controversy about the management of hepatitis C in pregnancy. A recent study evaluated the effect of the mode of delivery and infant feeding on mother to child transmission of the hepatitis C virus.³⁰ This group did not find a difference in transmission rates of hepatitis C with elective caesarean section or breast-feeding, unless the mother was also HIV positive. This study did not control for treatment of HIV, or hepatitis C RNA titres. In general, these mothers should have a normal delivery and be encouraged to breast-feed their infants.

Natural history of hepatitis C

It is now clear that the natural history, prognosis and clinical significance of chronic hepatitis C are variable. Chronic persistent infection is defined as hepatitis C-RNA positivity >2 years for infants, and >6 months for children >2 years. Data from adult studies indicates a high degree of chronicity with approximately 50% developing progressive liver disease and 20% developing cirrhosis 20–30 years after infection. Although there is considerable variation in disease outcome, chronic liver disease is more likely with genotype 1B.¹

Natural seroconversion is between 20%–40% in children infected by blood products^{31,32} compared to only 10% of vertically infected infants.³³

Acute hepatitis C is uncommon in childhood,³⁴ and most chronically infected children are asymptomatic with normal growth and development. There is little biochemical evidence of liver disease, but the majority will have chronic hepatic inflammation with a minority progressing to fibrosis or cirrhosis in childhood—particularly those with multiple transfusions or an underlying disease such as thalassemia.³⁵

In view of the adverse outcome detected in adults, it is important to regularly monitor children with hepatitis C to detect natural seroconversion and hepatic dysfunction to select children with persistent infection for anti-viral therapy.

Management of chronic hepatitis C infection

As for hepatitis B, children with chronic viral hepatitis C should be referred to specialized centres for information, counselling and family support. Annual reviews for children include detection of natural seroconversion, evidence of progressive liver disease and consideration for antiviral treatment (see Box 1).

Selection for treatment is based on the combination of persistent infection and evidence of histological disease.

Treatment for hepatitis C

Treatment for hepatitis C is based on combination treatment with Interferon (3 M units/m² subcutaneously ×3 weekly) and oral Ribavirin (15 mg/kg). There are many trials in adults, but a recent open multicentre study in children demonstrated that there is a sustained response rate of 45% for all genotypes with response rates of 70%–80% for genotypes 2 and 3.³⁶

More recently, a 6-month course of the combination of Pegylated Interferon (a long-acting Interferon which only needs to be given weekly) and oral Ribavirin has lead to 100% sustained viral response in both adult and paediatric patients with genotypes 2 and 3. Response is still less in patients with genotype 1 and only 50% responded after 12 months.³⁷

Liver transplantation for hepatitis C in children is rarely required, but it is a common indication in adults. Reinfection of the graft is almost 100%, despite prophylactic measures such as treatment with antiviral agents and modification of immunosuppression.²⁰

Future therapy for hepatitis C

Emerging new therapies include viral enzyme inhibitors, cytokines, antisense oligonucleosides but these are currently at an early stage of development.

Implications for paediatricians

The management of chronic hepatitis B and C in asymptomatic children in childhood remains a challenge. It is essential that children with either disease should be referred to specialized centres to benefit from counselling, information and for inclusion into multi centre trials of anti viral therapy in order that natural history and outcome of treatment be appropriately monitored.

Competing interests Professor Kelly has carried out a number of multicentre trials of therapy for both viral hepatitis B and C with GlaxoSmithKline¹⁵ and Schering Plough.^{6,36} She is currently undertaking a multicentre trial of Adefovir Dipivoxil for hepatitis B sponsored by Gilead Science.

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