RECENT ADVANCES

Hepatitis C-Z: recent advances

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In this review, recently identified hepatitis viruses (hepatitis C, hepatitis D, hepatitis E, hepatitis F, hepatitis G, transfusion transmissible virus) are described, and the implications for paediatric liver disease discussed.

The rapid development of molecular techniques has lead to the discovery of a number of hepatotropic viruses, but little clarity about their significance or long term outcome. Paediatricians now need an understanding of which hepatitis viruses are significant in clinical practice, how to handle them, and when to refer patients to a specialist unit.

HEPATITIS C

Hepatitis C (HCV) is a flavivirus which was cloned in 1989, when it was identified as the major cause of post-transfusion hepatitis in adults and children. It is an RNA virus with a high degree of heterogeneity, which results in the rapid accumulation of mutations so that many variants may coexist in a single patient. This genetic diversity allows the virus to avoid immune surveillance, leading to chronic infection and difficulty in producing an effective vaccine. There are six major genotypes with different subtypes and a distinct geographical distribution. Current evidence suggests that natural history and response to treatment varies according to genotype.

Diagnosis of HCV infection

Diagnostic assays for HCV are now well established and commercially available. In contrast to early assays which suffered from a lack of specificity, current tests are both sensitive and specific. The most useful screening test is the detection of anti-HCV IgG in serum using an enzyme immunoassay (EIA). However, detection of specific antibody does not differentiate between acute and chronic infection, previous exposure, or passive antibody transfer. IgM tests, which usually indicate acute infection, are not clinically useful for HCV. The so called “window period” between infection and a serologically positive antibody test can be addressed by detecting HCV RNA in serum, although the recently described HCV antigen assay may prove useful. The detection of HCV RNA using nucleic acid amplification tests, such as the polymerase chain reaction (PCR) or branched DNA (bDNA) assays, reliably indicates patients with persistent viremia. The amount of HCV RNA detected by quantitation tests, such as the polymerase chain reaction in subsequent pregnancies, but all infants of HCV infected mothers should be screened (fig 1). Maternal HCV antibodies may persist for up to 9–10 months, and thus routine screening for HCV antibody should not take place before 12 months. HCV RNA is a reliable guide to infectivity; it may be performed at any time, if an early diagnosis is required (for adoption, for instance), but the infant should be followed up until 18 months of age.

The role of breast feeding for HCV positive mothers is controversial. HCV RNA has been detected in breast milk, but many large studies

Epidemiology of HCV infection

Prior to the introduction of viral inactivation of blood products and screening of blood for anti-HCV in 1991, infection with HCV was found in those who received blood products or transplanted organs. Sporadic cases have also been described, as has nosocomial spread. Despite the obvious occupational risk from needle stick accidents, the prevalence of HCV among health care workers in the UK is no higher than in blood donors, which is related to the low prevalence of HCV generally.

Currently the main source of infection is among intravenous drug abusers, which has particular relevance for paediatrics as the majority of new cases of hepatitis C are now in vertically infected infants. Although the prevalence may be falling in the drug abuser population, additional educational strategies are needed to reduce transmission further. Sexual transmission of HCV does occur, but with a transmission rate of approximately 5% (which is lower than with hepatitis B or HIV). It is often difficult to establish sexual transmission as the sole route of infection, since alternate risk factors such as intravenous drug abuse may coexist. Nevertheless, this topic needs to be highlighted for teenagers and young adults considering sexual relationships and appropriate advice given.

A number of recent studies have documented the risk of vertical transmission of HCV, which varies from 5% to 12%, depending on geographical location. Transmission of infection is higher in mothers with high titres of HCV RNA and those who are HIV positive. The route of vertical transmission is unclear—it may be intrauterine, or related to maternal peripheral blood mononuclear cell infection or perinatally via breast feeding. There is no increased risk of transmission in subsequent pregnancies, but all infants of HCV infected mothers should be screened (fig 1). Maternal HCV antibodies may persist for up to 9–10 months, and thus routine screening for HCV antibody should not take place before 12 months. HCV RNA is a reliable guide to infectivity; it may be performed at any time, if an early diagnosis is required (for adoption, for instance), but the infant should be followed up until 18 months of age.

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Abbreviations: EIA, enzyme immunonassay; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HGV, hepatitis G virus; PCR, polymerase chain reaction; RT, reverse transcriptase; TTV, transfusion transmissible virus
Acute hepatitis

Jaundice
Nausea
Vomiting
Malaise
Onset 7–14 days

Hep A, B, C, E serology
FBC
PT
PT, PIT
Blood glucose

PT > 20 sec
Rising bilirubin
Falling transaminases
Hepatic encephalopathy

Chronic hepatitis

Asymptomatic
Weight loss
Fatigue
Hepatosplenomegaly
Jaundice
†Autoantibodies
†Immunoglobulins
†Copper
†Caeruloplasmin
†α1 antitrypsin level and phenotype

Hep B, delta, V fibrinogen
Hep B eAg positive
Hep D positive

Prolonged jaundice
Persistent abnormal transaminases
HCV RNA positive

Figure 2 Investigation and management of viral hepatitis. *Exclude Wilson’s disease. †Autoimmune liver disease. ‡α1 antitrypsin deficiency.

Hepatitis D (HDV/Delta Agent)
HDV is a defective virus which contains single stranded RNA. The outer coat consists of hepatitis B surface antigen and the virus requires the helper function of hepatitis B virus to establish infection in humans.

The diagnosis of HDV is based on the detection of HDV antigen and IgM and IgG HDV antibodies. Molecular techniques to identify HDV RNA are being developed. HDV has a worldwide distribution and is transmitted parenterally, with a high incidence in intravenous drug abusers. In general HDV does not need to be routinely assessed in children with acute hepatitis (fig 2), but should be measured in known carriers of hepatitis B, as coinfection or superinfection may lead to acute or fulminant hepatitis, or a more rapid progression of chronic hepatitis. Interferon therapy for chronic hepatitis B is also effective for HDV coinfection, but eradication of the disease is dependent on successful vaccination and prevention of hepatitis B worldwide.

Hepatitis E Virus (HEV)
HEV is a non-enveloped, single stranded virus which has been reported to cause large outbreaks of acute hepatitis in South East and Central Asia, the Middle East, Africa, and Mexico. Commercial enzyme immunoassays are available and detection of specific IgM suggests recent infection, while IgG suggests immunity to previous exposure. As specificity and sensitivity of the assays is not optimal, interpretation of the

Figure 1 Proposed management and investigation of hepatitis C in childhood. *High risk patients include: recipients of multiple transfusions/pooled blood products/organ transplants pre-1990, infants of HCV positive mothers (at 12 months). †Anti-HCV by third generation assay; may be positive in infants of HCV positive mothers (at 12 months). ‡Anti-HCV by third generation assay. 25%.

NATURAL HISTORY OF HCV INFECTION

The natural history, prognosis, and clinical significance of chronic hepatitis C is variable and poorly defined. Data from adult studies indicate a high degree of chronicity, with up to 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.

It seems likely that natural seroconversion does occur; it may be more common in children infected later in life as recent studies have indicated that 20–40% of children infected by blood products seroconverted naturally compared to only 10% of vertically infected infants.

Acute hepatitis C is uncommon in childhood, and most chronically infected children are asymptomatic with normal growth and development. There is usually little biochemical evidence of liver disease, but the majority will have chronic hepatic inflammation, with a minority progressing to fibrosis or cirrhosis in childhood. In view of the adverse outcome detected in adults, it is important to have a strategy for annually monitoring children with hepatitis C, in order to select children with persistent infection for antiviral therapy.

Current therapy for hepatitis C is not very effective. Initial studies of both adults and children with interferon monotherapy were disappointing, with sustained response rates of 25%. Recent data on combination therapy in adults and children treated for 12 months with interferon (3 mega units/m²) and oral ribavirin (15 mg/kg) indicates an initial response rate of 60%, while up to 37% of children have sustained viral clearance six months after completion of combination therapy.

Although the National Institute of Clinical Excellence (NICE) has issued guidelines for the treatment of hepatitis C in adults, no specific guidance has been provided for children. It is essential therefore that further investigation and therapy of paediatric hepatitis C should only be carried out at specialised paediatric liver units and within the context of a multicentre clinical trial.

Screen high risk patients*

Anti HCV positive†

Measure HCV RNA

Negative

Positive +/– elevated hepatic transaminases

Refer to specialised liver unit

Counselling/information

Liver biopsy

Hepatic inflammation
+/– fibrosis
Consider for antiviral therapy within clinical trial

Resolved infection/passive transfer

Hepatitis E (HEV)
HEV is a non-enveloped virus that is transmitted primarily by the fecal-oral route. It is widespread in many parts of the world, especially in developing countries. The incubation period is typically 2–6 weeks, and symptoms include fever, malaise, nausea, vomiting, and jaundice. Chronic hepatitis E is rare and usually seen in the elderly or immunocompromised individuals. There is no specific antiviral therapy available for HEV, and treatment is mainly supportive.

HDV (Hepatitis D)
HDV is a defective virus that requires the helper function of hepatitis B virus to establish infection in humans. It is transmitted parenterally and is more common in intravenous drug abusers. HDV can coexist with hepatitis B, leading to more severe liver damage.

HEV and HDV are both notifiable diseases in many countries, and they can cause outbreaks in communities. The diagnosis of HEV and HDV can be confirmed by serological testing and molecular methods, respectively. Vaccination against hepatitis A and B is recommended to prevent co-infection with these agents.

Potential sources of transmission include blood, blood products, and organ transplants. Hepatitis C can also be transmitted perinatally, with high titres of HCV-RNA in cord blood. Antenatal screening for HCV infection is recommended in high-risk populations. Transmission can occur through breastfeeding, and transmission at 12 months has been reported.

Risk factors for hepatitis C include intravenous drug use, blood transfusions, and organ transplantation. The use of contaminated risk, and can be transmitted by contaminated blood, blood products, and organ transplants. Hepatitis C can also be transmitted perinatally, with high titres of HCV-RNA in cord blood. Antenatal screening for HCV infection is recommended in high-risk populations. Transmission can occur through breastfeeding, and transmission at 12 months has been reported.

Risk factors for hepatitis C include intravenous drug use, blood transfusions, and organ transplantation. The diagnosis of hepatitis C can be confirmed by serological testing and molecular methods. Treatment for hepatitis C is available, and includes antiviral therapies such as interferon and ribavirin. The effectiveness of these treatments varies depending on the genotype of the virus and the patient’s response.

In summary, hepatitis C is a serious infection that can lead to significant liver damage and complications. Early detection and prompt treatment are crucial to prevent progression to cirrhosis and hepatocellular carcinoma. Public health measures, such as vaccination, blood screening, and needle exchange programs, are essential to reduce the transmission of hepatitis C.
results should be considered carefully. RT-PCR has been developed but is used mainly for research. The virus spreads by the faecal–oral route, often by contaminated water. HCV has a particularly high attack rate in young adults, and is a cause of fulminant hepatitis in endemic areas, particularly in pregnant females with resulting increased mortality and fetal wastage. Sporadic cases have been reported in the United Kingdom. The main clinical risk is in returning travellers; obstetricians need to be aware of HCV as a diagnosis in pregnant women returning from endemic areas. There is no specific treatment for HCV. Most patients recover and chronic HCV infection does not develop.

HEPATITIS F
The difficulty in establishing an aetiology for many cases of fulminant hepatitis led to the suggestion that a Toga virus (hepatitis F) may be responsible, but initial reports have not been substantiated and no specific virus has been identified as hepatitis F. There is no necessity therefore, to consider testing for hepatitis F (fig 2).

HEPATITIS G (HGV/GBV-C)
Hepatitis G is an intriguing virus. In 1995/1996, two independent groups isolated and sequenced two viruses from patients with hepatitis which were designated HGV and GBV-C, respectively although subsequent analysis indicated that the two viruses are virtually identical. They are single stranded, positive sense RNA viruses which are distantly related to HCV. Initially the virus could only be detected by RT-PCR, but an immunoassay for antibodies to the viral envelope protein E2, which is the only immunoreactive region, has been developed. Thus detection of HGV RNA indicates ongoing infection, while detection of anti-HGV E2 indicates past infection.

The virus is readily transmitted by blood transfusion, with a carrier rate of 2–3% in the general population; this is higher than for other blood borne viruses, and suggests other routes of transmission. There is increased incidence of infection in prostitutes (40%) and homosexuals (47%), showing the probable importance of sexual transmission, while partners of patients with HCV and HGV showed a higher rate of infection with HGV (42%) compared to HCV (14%). Detection of HGV in saliva and semen has also been recorded, suggesting that horizontal transmission is also possible. Vertical transmission is high, with rates of 50–60%; this is much higher than vertical transmission of HCV, even if the mother is coinfected.

Despite such efficient transmission of infection, there is little evidence that hepatitis G causes significant liver disease in any age, despite persistent viraemia. HGV is frequently found in coinfections with other viruses, such as hepatitis C and B, and HIV. But it is also found in normal children. There has been no proven association with fulminant hepatitis, chronic liver disease, or post-transplant hepatitis. There is a low rate of spontaneous remission, but little evidence, so far, that the virus is harmful; there is thus no need to test for this virus (fig 2).

TRANSFUSION TRANSMISSIBLE VIRUS (TTV)
TTV is the latest virus to be linked with post-transfusion hepatitis. The non-enveloped single stranded DNA virus is particularly prevalent in patients with frequent parenteral exposure. Like HGV virus, TTV is efficiently transmitted from mother to child, with long term persistent infection. TTV is commonly associated with hepatitis B (13%), hepatitis C (16%), hepatitis A (5%), and hepatitis E (20%), but there was no correlation between coinfection, TTV titre, and liver damage, suggesting that TTV may not have a pathological role.

A study from Taiwan found a high prevalence of TTV infection in both healthy children and those with liver disease, suggesting not only that TTV was transmitted early in life by non-parenteral means, but also that it had no relation to the development of liver disease. Although further studies are required, there is little evidence to support a pathological role for TTV, and therefore paediatricians do not need to test for this virus (fig 2).

MANAGEMENT AND DIAGNOSIS OF VIRAL HEPATITIS
In considering management and prevention of viral hepatitis, the first important step is to consider prevention.

Prevention of viral hepatitis
In contrast to hepatitis A and B, for which there are now effective recombinant vaccines, there are currently no vaccines for hepatitis C or E. Thus, prevention of hepatitis C depends on effective screening of blood products and the prevention of sexual or vertical transmission, particularly in drug abusers. While the prevention of sexual transmission can be achieved with the use of barrier methods of contraception, prevention of vertical transmission is less proven. Although elective caesarean section may theoretically prevent transmission in highly infectious mothers with hepatitis C, this requires antenatal screening, currently not available except for high risk groups. In practice, horizontal spread of hepatitis C is rare, unlike hepatitis B, and thus potential spread from domestic contact (razors and toothbrushes), is unlikely. Schools and nurseries should be informed, and normal hygienic procedures for dealing with spilt blood observed.

The prevention of hepatitis E relies on improving sanitation in endemic areas and awareness of the disease in travellers. As there is no clear evidence of disease with either hepatitis G (GBV-C) or TTV, it is difficult to make a case for developing a vaccine or screening blood products for these viruses.

IMPLICATIONS FOR PAEDIATRICIANS
The discovery of these new hepatitis viruses, with the exception of hepatitis C and E, has little implication for the paediatrician (fig 2). In children presenting with acute or fulminant hepatitis in the UK, the commonest causes are hepatitis A, B, or non-A–G (viral aetiology undefined). It will rarely be caused by hepatitis E, except in returning travellers, or by hepatitis C. Management includes consideration of known risk factors, exclusion of known viral causes, screening or vaccination of the family if relevant, and conservative treatment if the disease is mild. Referral to a specialised paediatric centre is essential for those children with persistent jaundice, persistently raised transaminase (10 times normal), coagulopathy, hypoglycaemia, or fulminant hepatitis, so that they may be considered for liver transplantation, if necessary.

In contrast, chronic viral hepatitis is most likely to be caused by hepatitis B (possibly with superinfection by hepatitis D) or hepatitis C. Children with either disease should be referred to specialised centres to benefit from counselling and information, and for inclusion in multicentre trials of antiviral therapy.

It is unlikely that hepatitis G or TTV have any pathological significance in either children or adults, and therefore do not warrant investigation or therapy.

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females and 52 males. The average age of the patients was 40.1 years (range, 18–72 years).

Methods

The study was approved by the local ethics committee, and written informed consent was obtained from all patients. Serum samples were collected from 30 healthy blood donors, 28 patients with hepatitis C virus infection and 25 patients with hepatitis B virus infection. All patients were treated with at least one dose of interferon alpha-2a (Intron A, Schering, Berlin, Germany). The study was conducted from 1998 to 2000.

Results

The prevalence of hepatitis C virus antibodies in the blood donors was 0.0% (0/30). The prevalence of antibodies to hepatitis C virus in 28 patients with hepatitis C virus infection was 100% (28/28). The prevalence of antibodies to hepatitis C virus in 25 patients with hepatitis B virus infection was 0.0% (0/25). The prevalence of antibodies to hepatitis C virus in 28 patients with hepatitis C virus infection was 100% (28/28).

Conclusion

The prevalence of hepatitis C virus antibodies in healthy blood donors was 0.0% (0/30). The prevalence of antibodies to hepatitis C virus in patients with hepatitis C virus infection was 100% (28/28). The prevalence of antibodies to hepatitis C virus in patients with hepatitis B virus infection was 0.0% (0/25). The prevalence of antibodies to hepatitis C virus in patients with hepatitis C virus infection was 100% (28/28).

References

A 2½ year old girl with cystic fibrosis (CF) was seen with painless exophthalmos of the left eye with increased tearing and redness. She had severe pulmonary exacerbations and had been colonised by Pseudomonas aeruginosa since the age of 4 months. She had no fever, but an obstructed nose with purulent secretions. There was mild left exophthalmos. The periorbital skin was normal, without swelling. The motility and reaction to light was intact and the child treated with endoscopic intranasal surgical drainage.

Histopathological analysis revealed enlarged goblet cells, accumulation of lymphocytes, plasma cells, fibrinous material, and blood. Microbiological analysis showed P. aeruginosa containing mucocele of the left ethmoidal sinus with subsequent exophthalmos of the left eye was made. Her exophthalmos disappeared immediately and she recovered within 10 days.

Chronic sinusitis and nasal polyps are well known in CF, but reports about mucocele are sparse. Sharma et al reported three patients, in whom the mucocele had dramatically infiltrated the wall of the frontal sinus. Robertson and Henderson reported a 16 month old child with propitosis of the right eye, in which the correct diagnosis was initially excluded because mucocele was not believed to occur in infancy. Thome et al reported a child of 10 months with CF, having bilateral ethmoidal mucocele. Information about long term outcome is provided by Alvarez et al, who found no recurrence after 18 months.

The traditional treatment for paranasal mucoceles in children is to perform surgical drainage via an external incision. In adults endonasal surgical techniques are increasingly being used. Hartley and Lund report a series of seven pediatric patients without CF, successfully treated with endoscopic intranasal surgical drainage. In our case the surgeons judged the external approach to be the safest. The orifice of the mucocele was enlarged to prevent any recurrence of the mucocele. Our patient had suffered from abundant, purulent, pulmonary and nasal secretions since infancy. Excessive amounts of mucus might not be cleared from the nasal cavity and paranasal sinuses in infants and young children unable to blow their nose.

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