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 hepatotrophic 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,[1] 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.[2] There are six major genotypes with different subtypes and a distinct geographical distribution.[3] 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).[4] 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.[5] The detection of HCV RNA using nucleic acid amplification tests, such as the polymerase chain reaction (PCR) or branched DNA (bDNA) assays, reliably identifies patients with persistent viraemia. The amount of HCV RNA detected by quantitation assays may be useful in determining infectivity and response to therapy.[6]

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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.[7] Sporadic cases have also been described, as has nosocomial spread.[8] 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.[9 10]

Currently the main source of infection is among intravenous drug abusers,[11] 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.[12] Sexual transmission of HCV does occur,[13] 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.[14–18] 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.[19] There is no increased risk of transmission in subsequent pregnancies,[20] 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,[21] but many large studies

Abbreviations: EIA, enzyme immunoassay; 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 transmissable virus

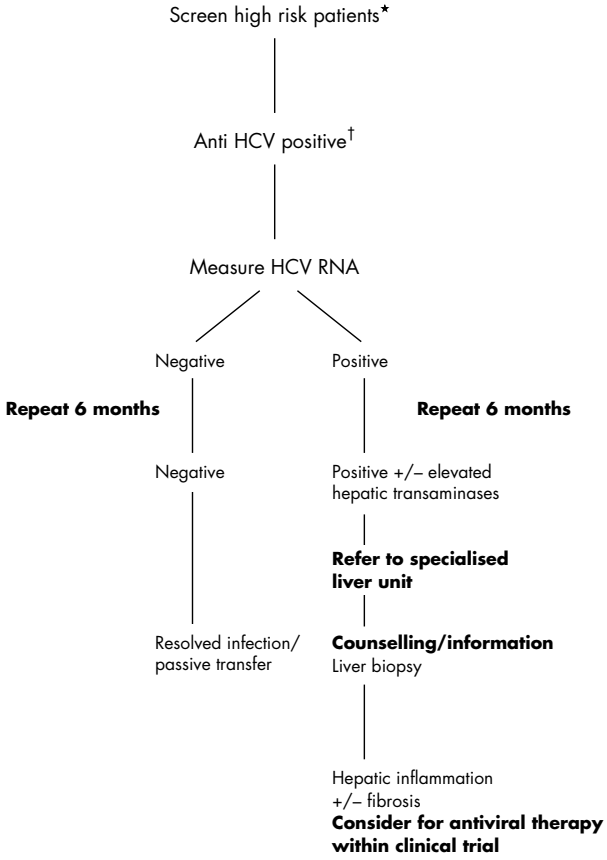

Figure 1 Proposed management and investigation of hepatitis C in childhood. *High risk patients include: recipients of multiple transfusions/pooled blood products/organ transplants pre-1990, infants of HCV positive mothers (at 12 months). †Anti-HCV by third generation assay; may be positive in infants of HCV positive mothers 9–12 months by passive transfer.

have shown transmission only in mothers with high titres of HCV RNA,[22] suggesting that it may be safe for most infants.

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.[23 24]

It seems likely that natural seroconversion does occur[25 26]; 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.[27]

Acute hepatitis C is uncommon in childhood,[28] 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,[29] with a minority progressing to fibrosis or cirrhosis in childhood.[30] In view of the adverse outcome detected in adults, it is important to have a strategy for annually monitoring children with hepatitis C (fig 1), 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%.[31 32] Recent data on combination therapy in adults and children treated for 12 months with interferon (3 mega units/m^2) 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.[33–36] Currently, treatment regimes are within the context of clinical trials in which only children over 3 years have been included. Of particular interest for paediatrics, is the development of pegylated interferon which is given weekly, and may be more effective than conventional interferon.[37] 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.

Clinical presentation	Investigations	Refer to specialist unit
Acute hepatitis		
Jaundice	Hep A, B, C, E serology	PT > 20 sec
Nausea	FBC	Rising bilirubin (> 100 µmol/l)
Vomiting	LFT	Falling transaminases
Malaise	PT, PTT	Hepatic encephalopathy
Onset 7–14 days	Blood glucose	
Chronic hepatitis		
Asymptomatic	Hep B, C, delta	Prolonged jaundice
Weight loss	FBC	Persistent abnormal transaminases
Fatigue	LFT	HCV RNA positive
Hepatosplenomegaly	PTT	Hep B eAg positive
Jaundice	† Autoantibodies † Immunoglobulins * Copper * Caeruloplasmin ‡ α_1 antitrypsin level and phenotype	Hep D positive

Figure 2 Investigation and management of viral hepatitis. *Exclude Wilson's disease. †Autoimmune liver disease. ‡α_1 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.[38]

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.[39] 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.[40] α 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.[41]

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

results should be considered carefully.[42] RT-PCR has been developed but is used mainly for research.[43] The virus spreads by the faecal–oral route, often by contaminated water.[44 45] HEV has a particularly high attack rate in young adults, and is a significant cause of fulminant hepatitis in endemic areas, particularly in pregnant females with resulting increased mortality and fetal wastage.[46 47] Sporadic cases have been reported in the United Kingdom. The main clinical risk is in returning travellers; obstetricians need to be aware of HEV as a diagnosis in pregnant women returing from endemic areas.[48 49] There is no specific treatment for HEV. Most patients recover and chronic HEV infection does not develop.[50]

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,[51] 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.[52 53] 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.[54]

The virus is readily transmitted by blood transfusion,[55] with a carrier rate of 2–5% 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%).[56 57] Detection of HGV in saliva and semen has also been recorded,[58] 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.[59 60]

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,[61 62] but is also found in normal children.[63] There has been no proven association with fulminant hepatitis,[64] chronic liver disease,[65] or post-transplant hepatitis.[66] There is a low rate of spontaneous remission,[67] but little evidence, so far, that the virus is harmful; there is thus no need to test for this virus (fig 2).

TRANSFUSION TRANSMISSABLE VIRUS (TTV)

TTV is the latest virus to be linked with post-transfusion hepatitis.[68] The non-enveloped single stranded DNA virus is particularly prevalent in patients with frequent parenteral exposure.[69] Like HGV virus, TTV is efficiently transmitted from mother to child,[70] 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.[71]

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.[72] 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,[73] 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 suprainfection 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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IMAGES IN PAEDIATRICS

Unilateral exophthalmos in a 2½ year old girl

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 mobility and reaction to light was intact and the child was able to fix with both eyes and to close the eye correctly. Fundoscopy was normal. A computed tomography (CT) scan was performed (figs 1 and 2). There appeared to be a tumour in the left orbit with erosion of the medial lamina, dislocating the bulbus anterolaterally.

Surgical intervention was performed and intraoperatively a fibrosing mucocoele was found and resected, together with the anterior and middle part of the ethmoidal cells. Histopathological analysis revealed enlarged goblet cells, accumulation of lymphocytes, plasma cells, fibrinous material, and blood. Microbiological analysis showed *P aeruginosa*. Diagnosis of a *P aeruginosa* containing mucocoele 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 mucocoele are sparse. Sharma *et al* reported three patients, in whom the mucocoele had dramatically infiltrated the wall of the frontal sinus.[1] Robertson and Henderson reported a 16 month old child with proptosis of the right eye, in which the correct diagnosis was initially excluded because mucocoele was not believed to occur in infancy.[2] Thome *et al* reported a child of 10 months with CF, having bilateral ethmoidal mucocoele.[3] Information about long term outcome is provided by Alvarez *et al*, who found no recurrence after 18 months.[4]

The traditional treatment for paranasal mucocoeles 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.[5] In our case the surgeons judged the external approach to be the safest. The orifice of the ethmoidal sinus into the nasal cavity was enlarged to prevent any recurrence of the mucocoele. 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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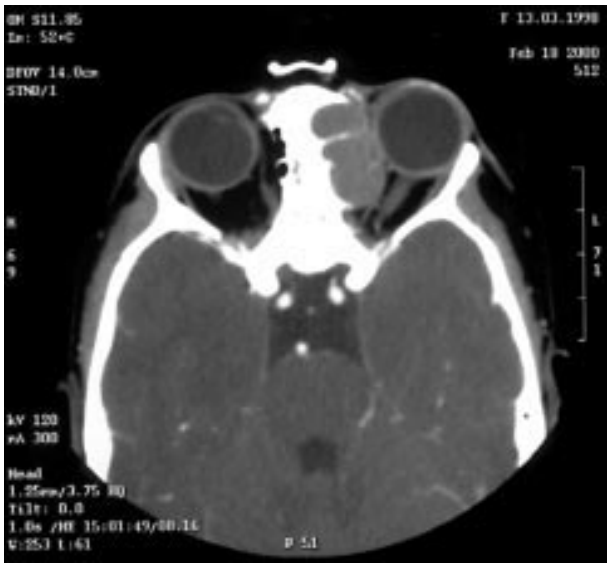

Figure 1 CT scan

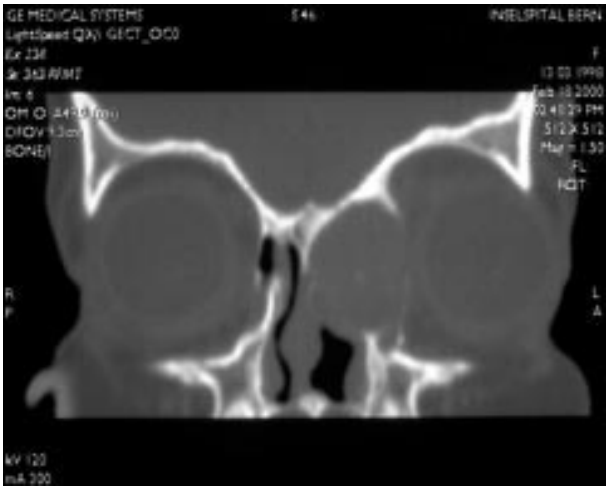

Figure 2 CT scan