Gastroenterology

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Update on viral hepatitis

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A summary of what is known about the transmission, prevention and treatment of all hepatitis viruses is shown in Table 1. This article focuses on the clinical features of the more recently described hepatitis C, E and G viruses.

Hepatitis C

Hepatitis C accounts for up to 90% of non-A, non-B hepatitis. It was discovered in 1989 by molecular cloning, and diagnosis by antibody tests has been available since 1991. It is a major cause of liver disease, cirrhosis and hepatoma in many parts of the world (UK 0.5%, Egypt 25%, Cameroon 40%), as estimated by anti-hepatitis C (HCV) immunoassay[1]. This infection has few specific features, but chronic fatigue is prominent. Anxiety regarding its mode of acquisition (eg from blood products) or potential transmission (to partners and offspring) often produces marked psychological stress. Hepatitis C progresses in a chronic indolent fashion in approximately 20–30% of infected individuals, usually taking up to 20–30 years for cirrhosis or any related complications to develop, but much more rapidly progressing cases have been documented[2].

HCV is transmitted efficiently by the percutaneous/parenteral route, but inefficiently by any other means. Important risk groups include people exposed to contaminated blood or blood products such as people with haemophilia or thalassaemia, but anyone who received blood products before routine testing became available in 1991 could be considered at risk. In Ireland and Germany, contaminated Rhesus anti-D immunoglobulin (Ig) administered intravenously has proved to be a source of hepatitis C infection. The use of non-sterile instruments and needle sharing among drug users is responsible for a large number of cases worldwide; previous intravenous drug use may account for more than 60% of cases in the UK. Health care workers appear to have a slightly increased risk. Sexual and perinatal transmission is thought to be an uncommon source, with a risk of 5–10% of infection from a partner with HCV.

HCV can be divided into six genotypes and a series of 40 definable subtypes because of variation in the genome of 9,000 ribonucleotide bases[3,4]. Intriguingly, it usually occurs in individual patients as a population of viruses with slightly diverse genotypes known as quasispecies. Genotypes 1a, 1b, 2a, 2b and 3a are common in blood donors and patients with chronic hepatitis C from Western Europe and the United States, whereas genotype 4 is common in the Middle East and Africa. Several clinical investigators have recorded severe and progressive liver disease after infection with each of the well characterised genotypes, but 1b is thought to respond

Table 1. Summary of viral hepatitis

Hepatitis virus	Transmission	Prevention	Treatment
A	Enteral	Sanitation Vaccine	Supportive
B	Parenteral Vertical Sexual contact	Screened blood Vaccine	Interferon Nucleoside analogues
C	Parenteral	Screened blood	Interferon
D	Parenteral with HBV	Screened blood HBV vaccine	Interferon Nucleoside analogues
E	Enteral	Sanitation	Supportive
G	Parenteral	Usual precautions	Not known
Seronegative	Unknown	Not practical	Supportive

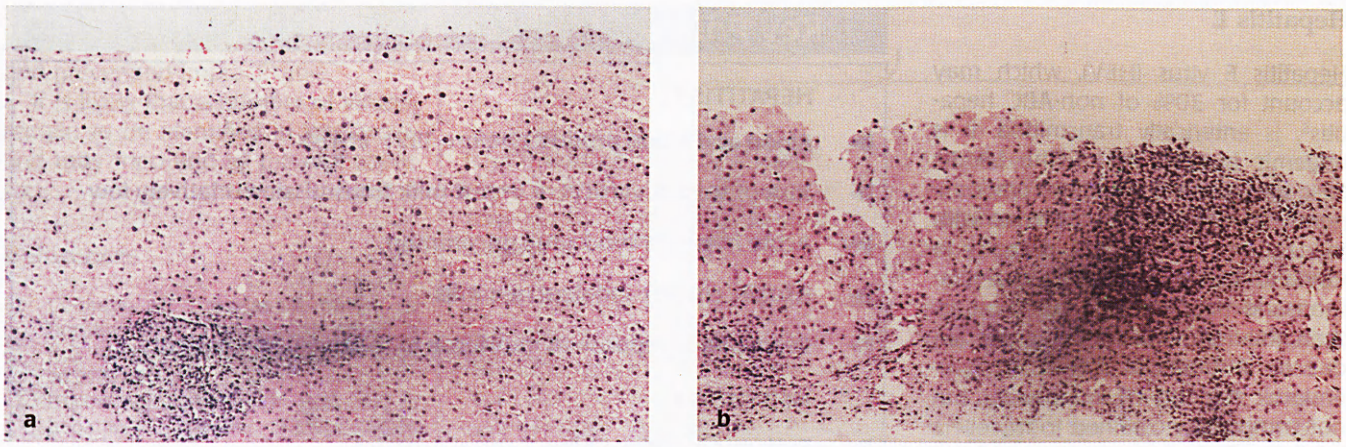

Figure 1. Photomicrographs of liver biopsies from two patients with hepatitis C infection showing the diversity of pathology: **(a)** mild to moderate chronic inflammation in portal tract with lobular hepatitis and microvesicular steatosis; **(b)** dense chronic inflammatory infiltrate with accompanying dense fibrosis and impression of nodular formation (probably cirrhosis); fatty change and spotty necrosis is also apparent.

less well to interferon (IFN) treatment than 1a, 2 or 3a. The incubation period is about 6–7 weeks, although acute infection often goes unrecognised. Only 10% of patients become jaundiced, and it is rarely a cause of fulminant hepatic failure. Hepatitis C recurs in patients following liver transplantation, but appears to progress less rapidly than hepatitis B in this situation.

Methods for detecting HCV have been evolving since its discovery, and earlier tests may have given a percentage of false-positive results. Currently, enzyme-linked immunoadsorbent assay (ELISA) kits detect antibody to two non-structural proteins and a core protein. In addition, strip immunoassays, which detect antibodies to two of the same proteins and two others, are sometimes used for confirmation. In combination with raised serum transaminases (alanine aminotransferase (ALT) or aspartate aminotransferase) or ultimately liver histology (Fig 1), they can be interpreted to confirm active infection. The use of reverse transcriptase polymerase chain reaction (RT-PCR) for amplification of the viral genome has greatly increased the ability to detect HCV and indicate the activity of infection. This is, however, expensive for routine screening and is used mainly to determine response to treatment. Branched DNA is an alternative quantitative method which can directly detect as few as 1,000 HCV genomes[5]. This is an amplification system employing branched oligonucleotides which contain a segment complementary to an HCV sequence covalently linked to a small alkaline phosphatase-labelled oligonucleotide.

Therapeutic options

Therapeutic options for hepatitis C infection are limited. IFN has been the mainstay of treatment to date. Less than 50% of patients have a biochemical response to treatment (normalisation of ALT) and far fewer become virus-negative in blood or the liver by PCR. Furthermore, there seems to be a sustained response in only about half of those patients who do show some response: overall, no more than about 20% of patients have a sustained response for 6–12 months after 3 MU of IFNα. Increased dose or duration of treatment seems to confer little additional benefit. Most centres offering this treatment limit it to periods of up to three months unless a detectable response in RNA level can be observed, in which case treatment is often continued for up to 12 months. Several non-genotype factors that may contribute to a better response to IFN are shown in Table 2. Response in individual cases cannot be reliably predicted, so restricting treatment to favourable subgroups remains controversial.

Ribaviran, a guanosine nucleoside analogue, may inhibit viral RNA polymerase and/or enhance macrophage inhibition of replication. Preliminary data suggest that it may confer additional and more prolonged benefit when used in combination with IFNα. Vaccines are currently not available for HCV, and their development is likely to prove difficult.

Table 2. Non-viral genotype factors which may contribute to a better response to interferon

- Younger age at acquisition
- Lower viral load
- Female gender
- Low body weight
- Absence of cirrhosis or significant fibrosis on liver biopsy
- Low serum ferritin or hepatic iron content
- Normal γ-glutamyl transferase and serum bilirubin levels
- Presence of cryoglobulinaemia

Hepatitis E

Hepatitis E virus (HEV), which may account for 30% of non-ABC hepatitis[6], is enterically transmitted. It is endemic in Asia, Africa, the Middle East and Central America, predominantly in developing countries with inadequate sanitation. Outbreaks in China and India have affected several thousand people, more often adults than children. One-third of cases are due to intrafamilial spread. In non-endemic regions, HEV is mainly, but not completely, confined to travellers returning from endemic regions.

The incubation period can be 15–60 days (most often 6 weeks) and, following a brief prodrome, the patient becomes icteric. Common symptoms include malaise, anorexia, nausea and vomiting, abdominal pain and fever. Diarrhoea, arthralgia and pruritus occur occasionally. HEV runs a self-limiting course in most patients, with resolution of serum bilirubin and transaminase levels in three weeks (range 1–6 weeks). It is thought not to cause chronic hepatitis, but fulminant HEV hepatitis has been reported in pregnant women with fatality rates of up to 25% in cases infected during the third trimester of pregnancy.

HEV was initially detected in the early 1980s using immune electron-microscopy. More recently, recombinant viral proteins have been used to produce antibodies which have been incorporated into enzyme immunoassays and Western blots. These can detect past or recent (IgM) infection in 95% of cases, although there are concerns that geographical variation in the virus may produce variable sensitivity in different outbreaks. RT-PCR can be used to study the natural history of the viraemia.

Therapeutic options

Treatment of HEV hepatitis is supportive. During an outbreak, interruption of spread by education and boiling drinking water is important. Prevention relies primarily on the provision of clean drinking water. The usefulness of post-exposure immune globulin to prevent infection is uncertain. A vaccine is not yet available, and it is unclear whether an effective vaccination strategy could be devised were one to become available.

Key Points

HEPATITIS C:

- Blood and blood products before 1991 'at-risk'
- Risk of sexual, vertical or breast milk transmission relatively low
- Acute hepatitis syndrome uncommon
- Usually chronic indolent hepatitis
- Permanent response to interferon in relatively few patients

HEPATITIS E:

- Endemic in India, China, Central America
- Enterically transmitted, intermittent epidemics
- Fulminant hepatitis during pregnancy

HEPATITIS G:

- Found in up to 2% of screened populations
- May not be a true 'hepatitis' virus

Hepatitis G

Hepatitis G virus (HGV), the latest addition to the hepatitides, was identified by two groups independently[7,8]. An inoculum from a jaundiced North American surgeon (initials GB) led to the identification of three closely related flaviviridae. GB-A and GB-B seem to be endemic in tamarins; GB-C was thought to have come from the inoculum, and it is 90% homologous with HGV isolated from a different patient with non-ABC hepatitis. Transmission is probably solely parenteral in contaminated blood products or by sharing contaminated needles and instruments. Co-infection with hepatitis B virus and HCV has been described, and it is unclear whether HGV infection can cause a clinical hepatitis syndrome – or even result in progressive liver disease – unless a co-infection is present[9]. Transaminase levels are elevated in about half the patients in whom virus is detected by PCR.

Diagnosis is made by detection of viral RNA by PCR. In pilot studies, approximately 2% of blood donors have been found to have this virus, and up to 20% of patients who receive regular blood products may be infected. An immunoassay for antibodies against an HGV protein has been developed very recently[10]; it is not yet widely available, and its clinical application not determined. Treatment is uncertain and may not be warranted.

Seronegative hepatitis

Non-ABCDEG hepatitis, the preferred term for which is seronegative hepatitis, accounts for approximately 10% of acute hepatitis cases. Recent studies indicate that these cases often have more severe jaundice and very high elevation of serum transaminases. Treatment is supportive,

and there is usually complete recovery[11]. Transmission is unknown and prevention impracticable.

It is likely that a number of viruses remain to be identified in this group and may then add to the alphabetic list.

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Acute liver failure

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Acute liver failure is one of the most challenging conditions to treat. Its outcome has been improved by a multidisciplinary approach that encompasses management in intensive care and liver transplantation. The treatment of acute liver failure may undergo further evolution if the newer extracorporeal systems prove to be effective in prolonging survival or acting as bridges to transplantation. A better understanding of its natural history has led to a revised categorisation of these patients and streamlined choice of management options. The new terminology uses the core term 'acute liver failure' which is prefixed by hyper- or sub- to describe the two ends of the temporal spectrum[1].

Terminology

Hyperacute liver failure: encephalopathy develops within seven days of the onset of jaundice. Paradoxically, this group has the highest likelihood of recovery with medical management, despite the characteristic rapid deterioration, high incidence of cerebral oedema and severe prolongation of prothrombin time.

Acute liver failure: encephalopathy develops 8–28 days after the onset of jaundice. This group has a high mortality, high incidence of cerebral oedema and marked prolongation of prothrombin time.

Subacute liver failure: the interval between the onset of jaundice and the development of encephalopathy ranges from 4–12 weeks. This state is also characterised by a high mortality, despite a low incidence of cerebral oedema and much less severe prolongation of prothrombin time.

Assessment of prognosis and monitoring

The most important management decisions are those concerning the need for referral to specialist centres and the indications for transplantation. Indications for transfer to specialist units for paracetamol overdose and other causes of acute liver failure are shown in Tables 1 and 2[2]. Separate criteria have been identified for use within specialist centres to identify the patients most in need of liver transplantation. The widely used King's College criteria[3] (Table 3) are early indicators of prognosis that do not rely on progression to the advanced stages of encephalopathy. In the original analysis, the discriminatory power of a metabolic acidosis with an arterial pH below 7.30 on the second or subsequent day after a paracetamol overdose was very strong (95% mortality), but the more liberal use of N-acetylcysteine and

Key Points

- Earlier referral and refinements of medical management continue to result in improved survival
- Liver transplantation options are widening through the use of auxiliary liver transplantation
- A new phase of interest in extracorporeal liver support may yield benefits in the near future