New agent to cause acute fulminant hepatitis ?

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In the developing world, acute hepatitis A, B and E virus infection are frequently observed, and may explain most cases of fulminant hepatic failure (FHF) and subacute hepatic failure (SAHF). In the United Kingdom and in North America, paracetamol poisoning remains the most common cause of FHF. However, the majority of poisoned patients survive, and few require liver transplantation. Other than cases of acute paracetamol poisoning, most cases of FHF and SAHF presenting in the developed world are of indeterminate origin (frequently called *seronegative hepatitis*). These appear to be associated with a poor prognosis, and hepatitis of indeterminate origin is now the diagnosis of more than 50% of patients transplanted for acute liver failure (1). For instance, in a consecutive series of 791 patients referred to the QEH for management of acute liver failure, 559 (71%) had paracetamol poisoning. Of the remaining 232 patients, 156 (67%) had acute liver failure of indeterminate origin. During this period, only 18 cases of acute hepatitis B and 8 cases of acute hepatitis A were referred. Of 166 patients with acute liver failure that underwent liver transplantation, 95 (57%) had acute liver failure of indeterminate origin. Thus, though the incidence of this condition is low, management of affected patients consumes significant resources including precious donor livers.

During the past 10 years, hepatitis C virus (HCV), hepatitis G virus (HGV), and transfusion transmitted virus (TTV) were discovered.

At the time of its discovery, HCV was the principal agent of post-transfusion hepatitis. Clearly, HCV is associated with acute and chronic liver disease, though reports of FHF due to HCV are frequently unconvincing. In 1991, Yanagi and colleagues reported an association of acute liver failure with HCV infection (2). Subsequently, many Western groups examined the association of acute liver failure with HCV infection, but few convincing cases were found (3). Superinfection of chronic HBV by HCV and coinfection of the 2 viruses may, however, be an important cause of acute liver failure (4,5).

A role for HGV and TTV as causative agents of acute and chronic liver disease has yet to be firmly established. As each agent was discovered, then followed numerous studies that examined the prevalence of infection in various populations, including those with cryptogenic chronic liver disease and patients with acute hepatitis and FHF. Concerning those patients with acute liver failure referred to the QEH, we were unable to confirm an association with HGV infection (6). Most studies have also failed to show an association of acute hepatitis (7,8,9,10), or acute liver failure, with HGV or TTV infection. Certainly, some have suggested an association of infection with acute liver disease, but evidence for causation is unconvincing.

In the case of HGV infection, for example, some studies showed that HGV RNA could be detected in the serum of FHF patients at the time of, or after, liver transplantation. Yoshiba and colleagues were the first to suggest an association of acute liver failure with HGV infection (11). It has also been suggested that variants of HGV may be associated with FHF (11,12,13). Heringlake and colleagues demonstrated an association of acute liver failure (including seronegative hepatitis) with the existence of a serine residue at amino acid position 34 of the HGV polymerase (12). This association was not confirmed by others (14,15,16). Also, serine34 is found in HGV-infected patients without liver failure. Thus serine34 is neither sensitive nor specific for acute liver failure. Other studies showed, however, that HGV infection is frequently acquired from transfused blood products during treatment of FHF (9,15,17,18,19). In many cases, sera collected at the time of hospital admission were HGV RNA negative. Thus, when the prevalence of virus-positivity in the general populaton (including blood donors) is quite high (as observed for HGV and TTV), the examination of pre-transfusion patient sera assumes importance.

Overall, it seems most unlikely that HCV, HGV or TTV are important aetiological agents of acute liver failure. It is possible, however, that infection may rarely cause liver failure in susceptible patients. Also, it is possible that some strains of these viruses may be pathogenic.

Thus, the search continues. It seems quite possible (even likely) that acute liver failure of indeterminate cause has many and varied causes. A viral aetiology is assumed and sought, but non-viral causes are also likely. For instance, use of non-steroidal anti-inflammatory drugs and herbal remedies which may cause acute

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hepatic necrosis is ubiquitous. Acute autoimmune hepatitis may be indistinguishable from other viral causes of acute liver failure. Clues to the aetiology of seronegative hepatitis might be provided by follow-up of patients who were successfully transplanted transplanted for this condition. For instance, the observation of unexplained acute or aggressive chronic hepatitis occurring the allograft might suggest recurrence of disease. Such pathology might not be expected to affect the transplanted liver of a patient who had experienced FHF as the result an idiosynchratic reaction to drugs or toxins. Graft hepatitis might reflect recurrent viral disease. We examined protocol post-transplant annual review biopsies of consecutive adult patients transplanted for seronegative FHF. Histological features were compared (in a blinded fashion) with protocol annual review biopsies of an appropriate comparison group (20). Only 1/42 seronegative FHF patients developed severe hepatitis with panacinar necrosis resembling the native liver pathology. However, chronic hepatitis was more likely to be present during follow-up of the seronegative FHF group, and hepatitis was of greater severity. Many developed significant graft fibrosis during post-transplant follow-up. Our observations are consistent with recurrent disease in the graft, and compatible with recurrent viral infection.

The aetiology of fulminant seronegative hepatitis remains unknown in the majority of cases.

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