EDITORIAL

Hepatitis C virus—epidemiology and serological diagnosis

In the 3 years that assays for antibody to hepatitis C virus (HCV) have been available, considerable progress has been made in our understanding of this infection.

Epidemiology

The high prevalence of anti-HCV found amongst intravenous drug abusers has confirmed that the parenteral route is the major route of infection. Another group with a potentially significant risk comprises patients who have received blood and blood products. However, the introduction of blood donor screening and heat treatment of blood products should have minimised this risk and testing of organ donors for anti-HCV is now routine.

Those at risk via the parenteral route also include patients on haemodialysis. The incidence of anti-HCV-positive patients in dialysis units in the UK varies but, generally, appears to be low, although this may not be the case in other countries. The rigorous application of measures designed to stop the spread of hepatitis B appear to have worked also for HCV. Most, if not all anti-HCV-positive dialysis patients have probably acquired their infection from blood transfusions and the number of positive cases should decline with the introduction of blood-donor screening.

All parenterally transmitted viruses represent a potential risk to health care staff. Avoidance of sharp accidents is an obvious precaution. When they do occur, current advice includes the immediate collection of blood samples from the inoculated person and the patient, if possible, for storage. This should be followed by screening for anti-HCV antibody approximately 6 months after exposure. Any illness that develops should be fully investigated. There is no indication that immunoglobulin preparations are effective in preventing HCV and, therefore, their administration is not recommended.

Finally, there is evidence that sexual and vertical transmission of HCV can occur although these appear to be relatively rare events.

Serological diagnosis

Improvements have been made in both specificity and sensitivity of tests for HCV and antibody, particularly with enzyme immunoassays (EIA). Increased sensitivity has led to the possibility of earlier diagnosis of infection although it remains 4–6 weeks after acute onset before serum samples become reactive in an EIA. Unfortunately, some non-specificity associated with EIAs remains and may still give rise to false positive results.

When an EIA-reactive sample has been identified, a repeat sample should be tested in both an alternative EIA and a supplementary assay before a diagnosis is reported, but even then results may be hard to interpret. Testing in an alternative EIA is recommended, but because different assays use different combinations of antigens, it is possible that a sample giving a true positive reaction in one assay may be negative by another, so limiting the usefulness of this approach. Furthermore, the supplementary assays utilise the same antigens as the screening assays and so cannot be regarded as true confirmatory tests. The most widely used supplementary assay is the “2nd generation” recombinant immunoblot assay (RIBA; Ortho Diagnostics) in which antigens 5-1-1, C100-3, C33 and C22 are blotted on to nitrocellulose strips; these represent the NS3, NS4 and highly conserved core region of the virus genome. A reactive sample is one that gives two or more bands of intensity at least equal to the low serum control band. If only one band is present, the result is designated “indeterminate”, the significance of which is open to conjecture. In patients with symptoms, or those who are asymptomatic but fall into a recognised risk group, a positive result in the screening EIA is likely to be specific, even if only an indeterminate result is obtained in supplementary tests. Problems arise when indeterminate results are obtained with serum samples from otherwise normal individuals; many such samples are from blood donors and there is obvious concern about how to report the results, given the implications of a positive result for the donor. The unnecessary loss of units of blood for transfusion is an additional problem. The polymerase chain reaction (PCR) has been used to try to determine whether samples giving indeterminate results, particularly those with either a C33 or C22 band, are truly positive. A proportion are found to be positive for HCV-RNA but a number remained unresolved and continuing studies will clarify the situation. In the meantime, patients who are RIBA “indeterminate” and HCV-RNA-negative by PCR should be followed carefully in the hope that improved tests will eventually provide a definitive diagnosis.

PCR technology is also being used in an attempt to determine whether patients who are anti-HCV positive are infectious. The detection of HCV-RNA is evidence of chronic infection. However, not all anti-HCV-
positive sera are PCR-positive, for which there are several possible explanations. A pattern of fluctuating viraemia has been described6 which may account for negative results with some samples. Alternatively, the level of viraemia may be too low for detection by current PCR assays. Storage and treatment of samples can have a deleterious effect on PCR results. The possibility also remains that a RIBA-positive, HCV-RNA-negative individual may have cleared the virus but whether permanently or not is debatable. Therefore, the present interpretation is that a positive PCR result obtained from a reliable laboratory indicates chronic infection and potential infectivity, but a negative result does not eliminate this possibility. A proportion of anti-HCV-positive, PCR-negative patients may prove to be immune and non-infectious, although cases of resolved HCV infection have been reported in which anti-HCV has become undetectable.7,8

Hopefully, some of the problems of HCV diagnosis will soon be resolved. Already a prototype third generation RIBA is being investigated with promising results9,10 and further improvements in testing should lead to better diagnosis and management of patients with HCV infections.

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Note added in proof. The RIBA 3 test is now widely available.

References