Hepatitis E virus and acute-on-chronic liver failure

Precise definitions are often lacking in scientific literature, and common medical conversation has had to tolerate without them. Time and again such ambiguity leads to problems of comprehension. For instance, the word ‘decompensation’ for most of us refers to the onset of jaundice and ascites in a person who previously had relatively asymptomatic liver disease. However, some have also used the term for a first variceal hemorrhage.¹

Acute-on-chronic liver failure (ACLF) has now, fortunately, been defined for us by Rajiv Jalan and his associates.² ACLF is described as acute deterioration in liver function over a period of 2 to 4 weeks in a person with previous liver disease. It is often associated with a precipitating event leading to severe deterioration in the clinical state, and usually presents with jaundice and hepatic encephalopathy and/or hepaticorenal syndrome with a high Acute Physiology and Chronic Health Evaluation (APACHE) or Sequential Organ Failure assessment score (SOFA). This understandably longwinded definition is open to criticism as it excludes those with minor deterioration. Yet, it is a good first step in the right direction.

This preamble on ACLF has relevance to two articles in this issue of the Journal.³⁴ Monga and colleagues³ from Delhi report that acute hepatitis E virus (HEV) infection in chronic liver disease – an obvious example of ACLF – is associated with high mortality. This echoes the findings of an earlier paper from our center in Vellore that demonstrated a two-third mortality in 9 patients with chronic liver disease and superadded HEV infection.⁵ In both these case series, however, the patients were identified because they presented with severe ACLF and had HEV in addition. No comparisons were made with patients with other forms of ACLF.

Kumar and associates⁴ from Lucknow have taken the opposite and more scientific tack. They prospectively studied patients with evidence of previous liver disease and jaundice – a not unreasonable clinical picture of ACLF. They found that 14 of 32 patients had acute HEV infection as a superadded event. In seeming contradiction to the previously mentioned papers, only 14% died. Although this mortality rate is higher than would occur with “stable” cirrhotic patients it is not like the rates reported in the other series alluded to above.

What do these conflicting data mean? HEV has had one unchallenged assertion made about it in the past. It has been incriminated, singularly of all the hepatotropic viruses, of causing a 20 percent mortality in pregnant women.⁶ This statement has not been questioned despite the fact that there are no comparable studies in other viral infections. Will these new data on HEV superinfection in chronic liver disease now make us believe that somehow HEV, of all the hepatotropic viruses, causes death more commonly in those with pre-existing liver disease?

There are two pieces of evidence against taking to such a belief readily. First, HAV superinfection has been shown to cause ‘fulminant hepatitis’ in patients with chronic hepatitis C infection, suggesting that this lethal effect is not unique to HEV.⁷ Second, our study had shown a high incidence of IgG antibodies against HEV in stable cirrhotics.⁵ The latter suggests that HEV infection can occur without devastating ACLF. Our study also picked up two patients with IgM antibodies to HEV, suggesting that acute HEV superinfection can occur without much fanfare. There was again a recent report, in Abstract form, showing that subclinical HEV infections do occur.⁸ To balance the record, we need to add that Saeed et al⁹ from Pakistan reported that patients with chronic liver disease in their hospital had evidence of past HEV infection that was no higher than in the general population. Therefore the behavior of HEV in chronic liver disease is far from clear. The best we can say at the moment is that HEV superinfection with severe ACLF probably has a bad prognosis.

The critical issue, therefore, seems to be the grade or severity of the ACLF. The Lucknow study fails to indicate how severe the ‘decompensation’ or deterioration in liver function was in their patients. Therefore, one wonders if the findings can be used widely and reliably. All scoring systems for assessing chronic liver disease, Jalan² informs us, are defective and inappropriate in ACLF. He recommends the SOFA system and it seems reasonable. It includes indices that measure liver function but also takes account of concurrent respiratory, cardiovascular, neurological and renal failure. Again without a study on the usefulness of SOFA in ACLF, we are still not on sure grounds. So, it is back to the drawing board and more studies on patients with ACLF and ‘stable cirrhotic’ controls, which will resolve these important issues.

We need not wait for the results of such studies to decide on advice to the cirrhotic patients we see in everyday practice. Hampered as we are without a vaccine against HEV, the only advice we can give patients is to ask them to ensure that the water they drink is clean and that no suspect fluids are taken in. Better hygiene has reduced the risk of hepatitis A in the West.
and in certain Indian situations. There is no reason why the same measures should not work with HEV. It may seem prudent to vaccinate patients with cirrhosis, except those due to hepatitis B, against both hepatitis B and A. However, almost all cirrhotics in India have antibodies against hepatitis A virus, an argument against using this vaccine in cirrhotics. This cozy picture will change with time when community hygiene improves.

Albumin dialysis has recently been shown to be beneficial in ACLF. In some situations it may only delay the need for liver transplantation. When transplantation seems to be the best therapeutic option, the optimum time for surgery will have to be defined.

All said and done, preventive measures seem more important than curative acts. Providing clean drinking water and active research to develop a vaccine should, therefore, be on the top of our priorities for HEV.

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References

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