

HEPATITIS E IN CHILDREN

Hepatitis E, previously known as enterically-transmitted non-A, non-B hepatitis, causes self-limited acute viral hepatitis, either as large epidemic outbreaks or as sporadic illness, mainly in developing countries of the Indian sub-continent, Asia and Africa. The first well documented epidemic of this infection occurred in Delhi in 1955-56 in which nearly 29,000 persons were estimated to have suffered from icteric hepatitis(1). Since then, there have been many epidemics of this infection in our country(2-7) and more recently, in 1991, we reported the occurrence of its largest epidemic in Kanpur affecting an estimated 79,000 icteric cases(8).

Hepatitis E is currently considered to be responsible for upto 53% cases of sporadic acute hepatitis in our country among adults(9). These presumptions were however based on the absence of serological markers of hepatitis A virus (HAV) and hepatitis B virus (HBV) infection in patients' sera. The agent responsible for this infection has since been identified, sequenced and cloned in the last few years and has been named as hepatitis E virus (HEV)(10,11). These developments have led to a considerable recent interest in this disease. However, this disease has not attracted much attention among the

pediatricians. In this editorial, we will, therefore, discuss various aspects of hepatitis E in children.

It was initially believed that hepatitis E only occasionally affected children. This was based on the observation during the Delhi epidemic that only 15% of all the cases seen were below the age of 15 years(1). Further, in a sample survey conducted during that epidemic, the incidence of hepatitis was only 0.21% and 1.75% among children in the age groups of 0-4 and 5-14 years, respectively as compared to 9.43% in young adults (15-34 years). These low attack rates in the presence of almost universal exposure due to massive contamination of the city's water supply with sewage led to the belief that the agent responsible for this infection for some reason spared children selectively. These findings of the Delhi epidemic were later confirmed in other large epidemics of hepatitis E(2,3,8). For instance, in an epidemic in the Kashmir valley, attack rate in children below the age of 10 years was only 0.5% as compared to 2.8% in the age group 11-40 years(3). In the large Kanpur epidemic, only 5.8% of all the hepatitis cases encountered in a sample survey were below the age of 10 years(8).

Although above observations would suggest that HEV infection was infrequent in children, it is possible that the infection may be occurring in children in mild and subclinical forms. Such a phenomenon is well known with hepatitis A infection, which occurs almost universally in children residing in

developing countries in a subclinical form leading to a life long immunity. Clearly, the situation is somewhat different in hepatitis E since its epidemics are associated with high attack rate in adults, which is difficult to explain unless the antibody is non-protective or wanes in adulthood. In the absence of definitive tests for diagnosis of hepatitis E infection, it is not possible at present to say which of these propositions is correct.

Availability of specific tests for the diagnosis of hepatitis E virus infection in the last few years has permitted a closer look on the important issue of hepatitis E in childhood. During the Kanpur epidemic, using reverse transcription-polymerase chain reaction, we demonstrated the presence of HEV genome in the stool specimen obtained from a child with icteric hepatitis(12); this definitively proves that HEV infection does occur in childhood. Later, Hyams *et al.* (13) using a Western blot assay showed that 23 (59%) of 39 Sudanese children (age range 2-14 years; mean 6.5) with acute viral hepatitis had IgM antibodies to HEV-specific peptides in their sera; acute HAV and HBV infections were responsible for only 33% and 3% of cases, respectively, and no child had evidence of mixed acute infections. Sixteen of the 23 children positive for IgM anti-HEV also had IgG anti-HEV antibodies. Among 39 concurrently studied controls, seven had IgG anti-HEV and three others had IgM anti-HEV. These findings suggested that HEV was the most common cause of acute sporadic hepatitis among Sudanese urban children. In a similar study(14), the same group of workers found that among 73 Egyptian children

with acute hepatitis, nine (12%) were due to acute hepatitis E infection whereas 41% and 4% were due to HAV and HBV and in 40% no cause could be found; two additional children had evidence of concurrent HAV and HEV infection. In another Egyptian study(15), 15 of 36 children with acute non-A, non-B hepatitis had IgG anti-HEV in their sera; of these 15, six had evidence of acute infection in the form of presence of IgM anti-HEV antibodies and two others had presumptive evidence of acute infection since IgG antibodies disappeared on follow up. On the other hand, only five of 20 controls had IgG anti-HEV and none of these had evidence of acute infection. These studies prove that HEV infection does cause symptomatic hepatitis among children and in fact is responsible for a significant proportion of acute sporadic hepatitis among them.

Similar data based on IgM anti-HEV antibody test from our country are lacking. However, as pointed out above, it is known that children do get affected during the hepatitis E epidemics though the attack rate for clinical hepatitis is not as high as in adults. A significant proportion (23% to 33%) of children with sporadic hepatitis do not have serological evidence of acute HAV or HBV infection(16,17) and a majority of them may be due to HEV infection.

How important then is it for a pediatrician in our country to diagnose hepatitis E infection and is specific diagnosis therapeutically important? Clinically and biochemically, acute hepatitis E and A are indistinguishable(16,18). Appropriate epidemiological setting and laboratory tests to detect the presence of

virus or antibodies to it are the only means to correctly diagnose the agent responsible for acute hepatitis. Presence of IgM anti-HAV in a child with acute viral hepatitis would suggest that hepatitis A is responsible for clinical illness whereas that of IgM anti-HEV antibodies would favor a diagnosis of acute HEV infection. The latter test, however is not perfect and its sensitivity and specificity are not exactly known. Other laboratory methods aimed at detecting the presence of virus (immune electron microscopy) or its genome (polymerase chain reaction) in the feces of patients with acute hepatitis are at present expensive and too complex for routine clinical use.

In the setting of an epidemic of hepatitis, it may be possible to distinguish the causative agent. Epidemics of hepatitis E are usually large and mainly affect young adults in the age group of 10-40 years and usually follow contamination of water supply(18,19). The disease carries a very high mortality rate among women in second and third trimesters of pregnancy (15-20%)(20). Epidemics of HAV on the other hand are unusual in developing countries like ours. Most of the population has exposure to HAV by the age of adolescence and is thus immune to this infection(21). Thus, children affected during an epidemic that predominantly affects adults may be assumed to be suffering from HEV infection. However, this may not always be true; route of transmission of HEV and HAV being similar, water contamination can lead to simultaneous spread of both the infections. One such mixed epidemic of hepatitis E and A was recorded in Hyderabad in 1990. In this

epidemic, 64% of subjects had evidence of non-A, non-B hepatitis (presumably hepatitis E) and 23% had evidence of acute hepatitis A. Almost all the cases of hepatitis A occurred below 10 years of age whereas non-A, non-B hepatitis affected both adults and children with a preponderance among young adults(22). Thus, epidemiologic setting of an epidemic affecting both children and adults may suggest, but does not definitely prove, that the illness in affected children is due to hepatitis E.

Attempts at specific diagnosis of acute hepatitis E are not really necessary except for research purposes since no specific treatment is yet available for this infection. In fact, no therapeutic intervention may be necessary for a disease as benign as acute hepatitis E. The disease generally has a self-limiting course and mortality rate in various epidemics has been below 0.1% except among pregnant women in the second and third trimesters of pregnancy.

Differentiation between these two common forms of hepatitis may, however, have significance with respect to prevention of spread of infection to others. Hepatitis A has a significant person-to-person spread(23). The infection rapidly spreads from one child to another in home or at school. On the other hand, intrafamilial spread is very uncommon in hepatitis E(24). Thus occurrence of hepatitis A in a child may necessitate more strict isolation procedures than that of hepatitis E. Further, in the last few years, effective vaccines against hepatitis A have become available^(^) and diagnosis of hepatitis A in one child may lead to a decision to vaccinate other children in the family.

No vaccine is yet available for protecting against hepatitis E infection and our current knowledge about immune response to an attack of this infection is too inadequate to predict long term protection. However, since infectivity of hepatitis A is the maximum in the preicteric phase and rapidly declines as jaundice appears, the role, if any, of vaccination in protecting other children in the family may be limited. Also, in a developing country like India where infection with HAV is so common, it is not clear whether vaccination against this virus will really be useful. Thus, even from a preventive standpoint there may not be much role for differentiating between HAV and HEV.

Thus, though hepatitis E infection in children does occur and appears to be commoner than was previously believed, it is frequently asymptomatic or mildly symptomatic. It has been shown to be an important cause of sporadic viral hepatitis in Africa and appears to be so in India. Though it is essential for all of us to be aware of this infection, routine use of tests for its specific diagnosis in children presenting with acute viral hepatitis may not be required since this information currently has no therapeutic, prognostic or prophylactic implications.

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