Natural history of chronic viral hepatitis in childhood

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Abstract

Chronic Hepatitis B virus (HBV) infection in children is commonly associated with Hepatitis B e antigen (HBeAg) seropositivity and histologic features of minimal to moderate hepatitis. Remission of liver disease is the rule following HBeAg to antiHBe seroconversion and clearance of HBV DNA from serum. In intermediate and low endemicity areas chronic HBV infection is usually acquired post-natally, and more than 80% of children are likely to achieve stable remission during the pediatric age. Severe sequelae, namely cirrhosis and HCC, have been observed only in less than 4% of children followed over two decades. In all cases cirrhosis was an early complication.

Chronic HCV infection is usually silent in children. The chronicity rate seems to be high (50-80%) in post-transfusion hepatitis C as well as in perinatally acquired infection. HCV-associated liver disease is characterized by fluctuations of ALT which remain below two times the normal in about half of the cases. Liver histology shows minimal to mild hepatitis in the large majority of patients and cirrhosis is rare. Few patients achieve spontaneous remission and progression to a more severe liver disease might occur in adult life. (Acta gastroenterol. belg., **1998**, 61, **198-201**).

Key words: hepatitis B, HBV, hepatitis C, HCV, hepatitis Delta, hepatitis G virus, cirrhosis.

Introduction

Hepatitis B (HBV) and hepatitis C virus (HCV) are the main etiological agents of chronic viral hepatitis in both adults and children. Infection of chronic HBV carriers with hepatitis Delta virus (HDV) is limited to endemic areas and its frequency seems to be declining, at least in the Mediterranean basin. Hepatitis G virus (HGV) has been recently described, but its role in the pathogenesis of liver damage remains to be clarified (1,2).

Natural history of hepatitis B

Infection of children with HBV is rarely followed by acute symptomatic hepatitis. This type of presentation is usually seen in older children and adolescents or in 3-month old babies born to anti-HBe positive mothers. In these latter cases fulminant hepatitis may develop (3,4). The chronicization rate of paediatric HBV infection depends on the mode of transmission and the time of infection. Vertically transmitted infection progresses to chronicity in more than 90% of cases and infection acquired during the first 5 years of life is thought to chronicize in 20 to 30% of cases (5,6).

The natural history of chronic HBV infection in children is characterised by an initial phase of tolerance to the virus, which can last few months to several years. The tolerant patient has high levels of HBV DNA in serum, is HBeAg positive and has normal or slightly abnormal ALT. The subsequent immuneclearance phase, which is in turn of variable duration, is characterised by an ALT increase which indicates the development of host immune response to infected hepatocytes. The reasons why a previously tolerant patient eventually develops immune competence, whether host or virus dependent, remain to be clarified. The immune clearance phase terminates with HBeAg to anti-HBe seroconversion which is often preceded by an increase of HBV DNA levels and an ALT peak, sometimes mimicking acute hepatitis. The subsequent remission phase is associated with the clearance of HBV DNA, as detected by the common hybridization techniques, the persistent anti-HBe seropositivity and the normalisation of ALT. This phase is sustained over the years and could be life-long in a yet unknown proportion of cases. The eventual clearance of HBsAg is infrequent. In children born of HBsAg positive mother the tolerance phase may last several years. The rate of HBeAg clearance is less than 2% during the first 3 years of life, but increases subsequently (7). A study of Chan *et al.* including 111 children infected at birth, showed that only 33% had cleared HBeAg during the first 10 years of life (8). It is likely that many of these patients maintain replication up to adult life.

Children infected post-natally come often to observation during the immune clearance phase. Only 20 to 30% present non specific symptoms such as asthenia and anorexia. Jaundice is rare. The majority is seen during intercurrent diseases or after screening for familial infection or for adoption. ALT levels are variable and liver histology is consistent with mild to moderate hepatitis in the majority of cases. In 3 to 4% of children liver cirrhosis is detected by liver biopsy at presentation : cirrhotic patients are usually males, infected early in life and with acute onset of the illness (9). During infancy and adolescence more than 80% of children with hepatitis B seroconvert to anti-HBe (mean annual seroconversion rate during the first decade of follow-up : 15%) achieve sustained biochemical remission and remain asymptomatic carriers of HBsAg without apparent viremia and enzyme alterations (10,11). Liver histology shows marked reduction

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of the Knodell's index, and sometimes only residual fibrosis or normal liver. Thus the prognosis of hepatitis B acquired in childhood would be a favourable one during the paediatric age. However, 90% of patients remain HBsAg carriers up to adulthood, and 50% are still HBV DNA positive 10 years after anti-HBe seroconversion when viremia is measured by the more sensitive polymerase chain reaction (12). This finding could explain the persistence of signs of inflammation and necrosis in some liver biopsies taken more than one year after anti-HBe seroconversion in spite of biochemical remission, the reappearance of mild ALT alterations and, in few cases, the reactivation of viral replication and liver disease (13,14).

Mild ALT alterations, generally not exceeding twice the normal, can be detected occasionally or more than once in about 10% of cases followed for 10 years or more after anti-HBe seroconversion, in the absence of viremia detectable by commercial hybridization techniques and of other putative causes of liver damage. The cause of such phenomenon awaits explanation. Reactivation, defined as the reappearance of HBV DNA measured by routine tests and of liver damage after anti-HBe seroconversion and biochemical remission, occurs in 3 to 5% of cases. In the series of Padua reactivation occurred 3 to 9 years after seroconversion in patients aged 13 to 25 years (13). In two cases there was transient seroreversion to HBeAg and in one persistence of anti-HBe positivity in serum. In all cases the analysis of the precore region of HBV genome showed the presence of a mixed viral population including wild type virus and e «minus» mutant. Thus the selection of a mutant of the precore region could be implicated in the reactivation of liver disease at least in some cases. Generally reactivation is a transient event, but subsequent bouts can be observed in the same patient, thus the prognosis of the disease remains to be evaluated.

In the Mediterranean area anti-HBe positive hepatitis has become now a frequent mode of presentation of chronic hepatitis B in adults. The disease may be severe and in this case it is often associated with a mutation in the precore region of HBV (15). Few children develop anti-HBe positive hepatitis : those who come to observation with anti-HBe positive hepatitis have a good prognosis, independently of the presence of low levels of HBV DNA. These young children are likely to experience a protracted immune clearance phase and usually achieve sustained biochemical remission within 4 years of follow-up. Conversely about 3% of older children with HBeAg positive hepatitis who seroconvert to anti-HBe maintain abnormal ALT and fluctuating viremia and behave like the adult patients with anti-HBe positive hepatitis.

Liver cirrhosis remains an early complication of hepatitis B in otherwise healthy children in the Mediterranean area, rather than the end point of long-lasting liver disease. During the first two decades of life only 3 to 5% of children with chronic HBV infection have features of cirrhosis, diagnosed at presentation or few months later. The prognosis of the disease is severe as 30 to 50% of cases can develop hepatocellular carcinoma during the paediatric age. Periodical alphafetoprotein measurement and hepatic ultrasonography are thus mandatory in these patients.

Natural history of hepatitis Delta

The biochemical and histologic features of hepatitis delta in children are generally more severe than those of hepatitis B at first evaluation. ALT levels exceeding twice the normal are frequently seen and 12 to 26% of paediatric cases present with cirrhosis (16,17). In otherwise healthy children hepatitis Delta is frequently associated with anti-HBe rather than with HBeAg positivity and HBV DNA may remain undetectable by routine hybridization techniques. During the first 5 to 10 years of follow-up spontaneous biochemical remission is rare, nevertheless the clinical and histologic features of the disease tend to remain relatively stable. In our series a 3-year old boy with Delta-associated cirrhosis has been followed for 18 years without evidence of hepatic decompensation. These observations suggest that further progression and adverse events are likely to appear in adult life.

Natural history of hepatitis C

HCV infection is relatively infrequent in the paediatric age, with anti-HCV prevalence rates of 0.1-0.3% in the Western world (18). Higher prevalences were found in multitransfused children such as haemophiliacs and thalassemics, but there is evidence of declining rates even in these risk groups after the introduction of HCV screening. In fact, while 60% of otherwise healthy children observed in the early nineties had a history of blood transfusions received early in life, there is now evidence that vertical transmission is the main route for the spread of HCV infection in childhood, although the efficacy of transmission is low (19). This epidemiological pattern and the fact that paediatric disease is usually asymptomatic and thus was rarely diagnosed as non-A, non-B hepatitis before the introduction of HCV screening, explain why little is known to date on the long-term evolution of chronic hepatitis C acquired in childhood. Fig. 1 summarises the main features of infection and hepatitis C in children. Both post-transfusion and vertically acquired HCV infection seem to progress to chronicity in 60 to 80% of cases. Vertically acquired infection, confirmed by the presence of circulating HCV RNA in at least two serum samples during the first months of life is usually associated with ALT elevations of variable level since the third month of life. About 20% of cases normalise ALT and clear HCV RNA from serum starting from the second year of life (20). Whether these events, associated with the

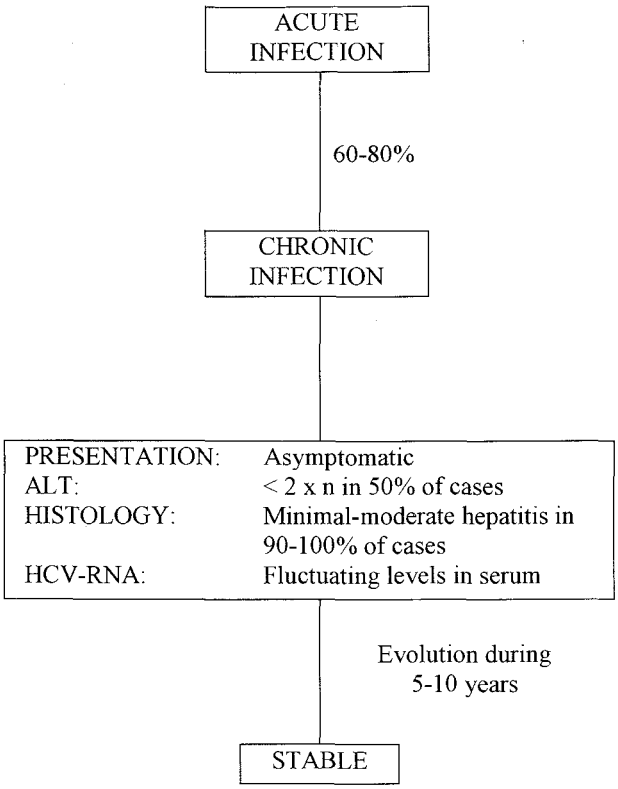

Fig. 1. — Features and evolution of HCV infection and associated liver disease in children.

persistence of anti-HCV, represent recovery or a silent phase of infection remains to be evaluated. The chronic phase of infection in both infants and children is asymptomatic and characterised by frequent fluctuations of viremia and ALT. About 10% develop antibodies to LKM1 at variable, usually low, titre (21). Extrahepatic manifestations are rare.

There are no apparent differences in the clinical course of post-transfusion and community-acquired hepatitis C, possibly because both are acquired early in life and genotype 1b is prevalent in both (22). Recently however, the epidemiological changes seem to support an increasing prevalence of genotype 3 infection among children of anti-HCV positive mothers, probably in relation to maternal drug abuse (23). In spite of its benign presentation chronic hepatitis C has a poor propensity for spontaneous remission : less than 10% of cases present sustained ALT normalisation during the first 5 years of follow-up. Liver cirrhosis is rare but a recent analysis of 80 liver biopsies of children with hepatitis C and no underlying diseases shows that there is a correlation between known duration of infection and degree of fibrosis, suggesting that more severe manifestations of the disease could appear in adult life (24).

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