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The natural history of vertically acquired HCV infection

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The World Health Organization estimates that about 3% of the world population is infected with HCV and 3 million individuals are infected each year. Most of those infected develop chronic liver disease leading, in some cases, to liver failure or hepatocellular carcinoma.

Little information is available on the epidemiology, natural history and responsiveness to antiviral therapy of HCV infection in children. The epidemiology has changed substantially in recent years. In Italy, for example, in the 90's most children were affected by post-transfusional hepatitis. In contrast, in the new millennium most have been due to mother-to-child transmission. The total number of vertically infected children has also been decreasing, because the screening of blood donors has reduced the spread of the virus to women of child-bearing age. However, in the USA approximately 7000 new cases of vertical infection are estimated to occur over the next decade. The screening of blood donors has also changed the relative prevalence of different genotypes in infected children, with a decrease in transfusion-associated type 1b genotype and an increased percentage of genotypes 3 and 4; this has relevant therapeutic implications since the latter are more sensitive to specific treatment. Newer population-based studies on the epidemiology of paediatric infection in different parts of the world are needed.

During primary infection no vertically infected infant becomes icteric or developed signs. Interesting, only one third of infected infants are viraemic at birth. The PCR assay proved highly specific with a good sensitivity (about 80%) from the first month of life. Based on the presence of viraemia over time, three groups of vertically infected children can be identified: a) with persistent viraemia, b) with intermittent viraemia, and c) seropositive children in whom serum HCV RNA was never detected. At times, children with intermittent viraemia may be PCR-negative but with increased ALT levels. Initially, ALT levels mirror a primary infection that is normal or mildly enhanced values during the first months of life, with a subsequent increase. ALT concentrations decline after the first two years of life, presumably reflecting better viral control by a more effective adaptive response after infancy. Overall, the enhancement of ALT levels was less frequent and pronounced than in adults.

HCV-associated clinical manifestations were observed in a minority of vertically infected children, with only a quarter developing hepatomegaly in the first decade. Furthermore, all children grew regularly, with no variations from the normal height and weight ranges. A high frequency of autoantibodies has been reported also in childhood, although with the bias of a selected population recruited by tertiary care centres, while the incidence of autoimmune reactions in vertical chronic infection remains to be established.

Wide ranges of histopathologic abnormalities have been found in children with vertical infection. Although to different extents, most patients had signs of chronic hepatitis. Based on signs of structural alterations, inflammatory activity, and necrosis the grade of disease usually varies from minimal to moderate, though some children have a certain degree of fibrosis. No direct correlation was found between underlying liver disease and increased ALT levels, suggesting that these are not accurate prognostic markers. Some cases of advanced liver disease in infected children have however been described, including the need for liver transplantation. In general, patient and allograft survival are suboptimal in transplanted children with chronic HCV infection, with a high risk of recurrence requiring retranplantation with a poor prognosis.

Taken together the data suggest that about 20% of vertically infected children, being repeatedly PCR negative the last times they were tested, with no symptoms or ALT abnormalities, apparently recover from infection. Half of the children remain asymptomatic with chronic infection, fluctuations of viraemia and ALT activity. The remaining 30% have chronic active infection with persistent viraemia, abnormal ALT activity and, sometimes, hepatomegaly. Among these a fraction may develop severe liver damage.

This heterogeneity in disease progression implies the existance of virus-related and/or host-related factors conditioning the liver injury, which require specific research. Most studies agree that genotypes and viral load do not have a significant impact on the evolution of infection, although some authors suggest a worse outcome with genotype 1. Several investigations focused on the diversification of HCV quasispecies in vertically infected children. In general, only one or a low number of variants are present in the first months of life, then seroconversion leads to the development of many quasispecies. The pressure due to the humoral response is consistent with the low or no viral diversification observed in hypogammaglobulinemic subjects, who have severe disease progression. In one study, biochemical evidence of hepatic injury was invariably associated with a mono- or oligoclonal viral population, whereas mild or no liver damage correlated with the early emergence of many viral variants.

As far as host-related factors on HCV progression are concerned, many immunologic alterations in both PBMCs and in the liver have been described. However, these findings mostly seem secondary to the chronic infection rather than being responsible for its evolution.

In conclusion, vertically-acquired HCV infection is characterized by a high chronicity rate, but mild liver injury for most of those infected. This supports the hypothesis that the hepatocellular insult is not due to the direct cytopathic effects of HCV, but rather to the virus-driven immune response. The less vigorous reaction of the immune system in the first years of life may be insufficient to eradicate the virus completely, although it may account for the lower liver damage. The virus interacts with the immune system to guarantee its survival, but, unlike HIV, it leaves the host free to control other infections. Given the lack of clinical manifestations, children with chronic HCV infection may remain undiagnosed until the late appearance of symptoms and signs in adolescence or adulthood, when therapeutic interventions may less efficiently prevent or eliminate long-lasting liver damage.