Viral hepatitis throughout infancy to adulthood

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Introduction

Pediatric hepatitis B or C carriers are most often asymptomatic, at least for the first decade, and the disease progression is slow, with an average of twenty to forty years before the onset of clinical liver disease. For these reasons, many B or C carrier children are not brought to the attention of specialist physicians, and they thus miss appropriate counselling and treatment options. Adolescents may not be willing to attend medical clinics. At the same time, at risk behaviour starts, not only for transmission of hepatitis virus, but also for superimposed liver injury such as alcohol intake. Another decade may pass before the young adult will take care of his personal health, most commonly when starting a family and/or applying for life insurance. At that time, the young adult may have cleared hepatitis B, less frequently hepatitis C. Questions are raised regarding materno infantile and inter-spouse transmission. Persistantly infected patients may start to experience clinical problems, finally becoming candidates for liver transplantation. Liver cancer may be found in these patients.

The aim of the meeting held in Brussels is to review these different stages of viral hepatitis, from infancy to adulthood, and to promote continuity in the clinical and therapeutic follow up of these patients between pediatricians, general practioners and internists. This article reviews the main questions relative to hepatitis A, B and C in childhood and adolescence.

Hepatitis A

Hepatitis A has become rare in developed countries as a result of improved hygiene, and less than 10 to 20% of young adults are naturally immune (1-7). The consequence is, however, that outbreaks may occur, and easily spread in this non immunised population. The disease may be fatal to young children, and it is one of the main causes of fulminant hepatitis in paediatrics (8,9). Mortality is low in adolescence and young adulthood, but beyond fifty years of age, mortality following hepatitis A reaches 2.7%: Such a high mortality rate in a population with less and less natural immunity may become problematic should epidemics occur following breakdown of public hygiene.

To present, vaccination has been concentrated on risk groups, cost effectiveness studies do not favour systematic vaccination: vaccination is therefore concentrated on travellers, certain categories of workers, and patients with underlying liver disease (10,11). Patients with chronic hepatitis C seem to be particularly at risk of developing severe liver disease when HAV superinfection occurs (10,12,13). The vaccine is also effective in interrupting outbreaks inside a particular community (school, day care centres,...) (14). Future studies will determine whether today's selective vaccination policy can reduce morbidity and mortality due to hepatitis A.

Hepatitis B

Hepatitis B is the ninth cause of mortality in the world, and WHO estimates that 400 millions humans will be carriers of this virus by the year 2001. In numerous countries in Asia and Africa, active hepatitis B affects 10 to 20% of the population, and up to 50% have been in contact with the virus. In developed countries, on average 1% of the population are carriers. In the United States, 300000 persons are infected each year by the hepatitis B virus (HBV), and 5000 people dye every year from fulminant hepatitis, cirrhosis or hepatocarcinoma (15,16). In Belgium, 6% of the population has markers of previous contact with the virus (3,17), as compared with 5% in the United States (15). It can therefore be estimated that 200 Belgian citizens dye every year from hepatitis B. Post hepatitis B cirrhosis is in addition one of the most frequent indication for liver transplantation, necessitating after surgery an expensive program of long term immunoprophylaxis with hyperimmune gammaglobulins to prevent viral recurrence (18,19). Hepatitis B virus causes hepatocarcinoma more than hepatitis C virus, most commonly in cirrhotic patients, but also in healthy carriers, and this complication is also described in childhood (20-23).

Despite the availability of an efficient vaccine since the early eighties, the prevalence of hepatitis B has not decreased significantly worldwide, although significant reduction and quasi eradication of this infection is feasible through mass vaccination programs (15,23-28). In Taiwan, mass vaccination decreased the incidence of HBs ag carrier rate in children from ten to one

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percent, and simultaneously decreased significantly the incidence of childhood liver cancer (23).

In Belgium, access to vaccination remains very limited, and the current strategy is not likely to decrease the incidence of disease : Strikingly, public health organisms have decided to allow free vaccination for infants, but not for adolescents who are probably the most sensitized to the problem, being also the group at highest risk. In addition, the incredibly heavy Belgian administrative requirements to obtain refunding refrain access to immediate vaccination of the child during a routine visit.

The progression of chronic hepatitis B acquired in childhood is usually mild during the first two decades, and a significant proportion will clear viral replication before adulthood (29). The aim of treatment is to shorten disease evolution by favouring HBe ag to ab seroconversion. Treatment is indicated in children with elevated transaminases and active viral replication. Precise guidelines for alpha interferon treatment in children were proposed by the Madrid 1997 working party (30). Treatment of hepatitis B with interferon in children as in adults yields a success rate of 20 to 40% in obtaining viral replication loss (loss of HBV DNA and HBe ag) (31-43). HBs ag loss is more frequent after interferon induced than natural HBe seroconversion (39). In adults and in children, loss of viral replication is followed by an improvement of biochemical, histological and clinical outcome. The treatment is able to prolong life expectancy and decrease disease related cost in young adults (37,39,44-46). There is still controversy in children about higher success rate in patients with high transaminases. In the largest pediatric randomized controlled multicentric trial, the highest benefit from treatment was obtained in female children, with intermediate DNA levels (between 10 and 200 pg/ml, Abbott radioimmunoassay). Children with low DNA (< 10 pg/ml) had a high percentage of spontaneous seroconversion, and children with very high DNA had a poor response (39). Transaminase levels were not of prognostic significance, but only children with elevated transaminases had been included. Other studies did not show differences in response rate according to basal transaminases (38).

Steroid priming has not been shown to be as useful in children as in adults (34,47-50). New treatments with nucleoside analogues are promising, and Lamivudine and Famcyclovir are currently being tested in children. Although these drugs are efficient inhibitors of viral replication, their ability to induce HBe ag to ab seroconversion remains limited, and rebound of viral replication occurs when treatment is stopped (51). These drugs are currently used in transplant recipients with hepatitis B recurrence on the graft, including children, but escape mutants may emerge during therapy (52,53). Future strategies will probably use combinations of these drugs alone, or with interferon or hyperimmune vaccines (41).

Hepatitis C

Should hepatitis B be controlled by mass vaccination, hepatitis C virus will still cause death from chronic liver disease and liver cancer. Eighty five percent of infected persons will develop chronic liver disease. Chronic hepatitis C has a slow pattern of evolution, and most children will be asymptomatic for at least two decades, with mild to moderate histological changes (54-56). It is important to protect chronic hepatitis C carriers against any additional aggression to their liver. The disease evolution is accelerated by alcohol consumption, or superimposed infections, particularly hepatitis A, and there is probably a synergistic effect of any other associated liver sickness (10,57). In particular, coinfection with hepatitis B and C has a synergistic effect on the risk of hepatocarcinoma (20). The disease may slowly progress to end stage liver disease, and hepatitis C has become one of the main indications of liver transplantation in young adults in the western world. This virus is found in 0.6 to 0.8% of the Belgian population, and in 0.5 to 2% of Europeans (58). Transfusion of blood products before screening of blood donors (1990 in Belgium) is currently the main cause of chronic hepatitis C in adolescence. Systematic screening children/adolescents at risk shows that 10 to 15% on average may have been contaminated and systematic screening is desirable in patients who belonged to the following groups (not exhaustive) : exsanguino transfusion in the neonatal period, thalassaemia major, haemophilia, leukaemia, bone marrow transplant recipients, cardiac surgery, liver and kidney transplant patients, or any other multi-transfused patient (54,59-67). Spontaneous remission (normalisation of transaminases and loss of HCV serum RNA) was described in 4 of 48 (8.3%) children with transfusion acquired hepatitis C. In one of them, HCV RNA was still detectable in the liver and the child eventually relapsed (68). Materno-infantile transmission is frequent if the mother is immunosuppressed, and is related to high viral load. Transmission is much rarer in immune competent mothers : 3 to 6% of their offspring will become carriers (69-76). Hepatitis C materno infantile transmission is exclusively described in HCV RNA positive women, and the risk of transmission is correlated with the level of viraemia. The risk is highest if the viral load exceeds 1×10^6 copies per millilitre, and appears to be limited below 10^5 copies per millilitre (67,72). Breast feeding is allowed and has not been shown to transmit the disease. The virus is present in breast milk, but at lower concentration than in plasma (67). Sexual transmission of hepatitis C may occur, but this mode of transmission seems to be rare between monogamous stable partners who can remain disease free for decades. It is possible that the risk of transmission increases with the duration of marriage (76-79). This mode of transmission may be more frequent in persons with multiple partners, history of

sexually transmitted diseases, and of low socioeconomic origin. Counselling practice for stable partners is not easy, but there is insufficient evidence of sexual transmission to propose systematic use of latex condoms. Sharing toothbrushes and razors should be avoided, as well as unprotected sexual activity in case of genital irritation and/or during menstruations.

Nosocomial transmission of hepatitis C, although limited, has been described (80), and up to 30% of hepatitis C carriers do not recall or declare a recognised source of contamination.

Treatment of chronic hepatitis C with interferon in adults leads to a 15 to 25% sustained response rate (i.e. normal transaminase and no detectable serum HCV RNA 6 months after the end of treatment). The usual scheme in adults is 3 million units, three times weekly, for six months. Prolongation of treatment to 12 months or more improves the sustained response rate (41,81,82). Daily administration of higher doses may improve response, even in advanced disease (59). Treatment is recommended for patients with abnormal transaminases (> 1.5 times upper limit of normal) and abnormal histology (81,82).

The best candidates are young, have a short duration of disease, absence of cirrhosis, low HCV RNA levels, low iron content, low gamma-glutamyl transpeptidase levels (83). Although genotype 1 B may be less favourable for response to interferon, it is anyway by far the most common in our population and is associated with progressive disease. This parameter is therefore not relevant for a decision to treat. Adjunction of Ribavirin to interferon increases the percentage of responders, and seems mainly beneficial in patients with high serum DNA. It does not seem beneficial in previous interferon non responders (84). This drug is currently not available for children. Its main side effect is to provoke haemolytic anaemia.

Retreament is not successful in non responders, but should be considered in responders who relapse subsequently (85). These latter patients may benefit from adjunction of Ribavirin to interferon (84).

Cost effectiveness studies show a higher benefit of treatment at younger age in adults, in relation to the longer life expectancy (41,45,81,82,86,87). No large pediatric trials have so far been published to allow comparison of response rate in children to that in adults (86). Many children are asymptomatic, and it seems reasonable to apply the same treatment criteria as in adults : abnormal transaminases and histology, with proven positivity of HCV RNA in serum. Children usually meet these criteria for favourable response, and a better overall response than in adults could therefore be obtained, although this remains to be demonstrated (83). Treatment should not be given to very young children, less than two years of age, in view of possible interference with growth during this high growth velocity period. There is probably no advantage to prolong treatment if HCV RNA persists in serum after three months. In responders, prolongation of treatment up to one year can be considered, with strict observation for side effects, including on growth velocity.

Unanswered questions

Major questions remain regarding specific aspects of chronic hepatitis B or C in children. Natural history remains insufficiently known, and no markers exist to identify subjects who will enter remission or are at risk for complicated liver disease. Natural history studies are extremely difficult to conduct over several decades, and most diagnosed patients will these days have one or more therapeutic attempts. Superimposed liver injuries may be insidious and are not always identified, and may markedly influence the spontaneous course. As far as treatment is concerned, efficiency is similar to that obtained in adults for HBV, and might be more favourable for HCV, which remains to be demonstrated. Indications for treatment do not really differ. The longer life expectancy, and hence duration of disease, should be considered. The precise timing — disease stage — at which to initiate treatment is not defined. Histology does not only reflects current disease activity, but also length of evolution, and similar histological findings should be interpreted differently in a child. Interferon is well tolerated by children, but should not be given to patients less than two years. It is clear that treatment shortens the disease duration in responders. Whether these responders belong to a group with a favourable or unfavourable natural outcome remains to be determined, in children as in adults.

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