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Pediatric Hepatology: Present and Future*

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Pediatric Gastroenterology was born as specialism within Pediatrics during the 1960s, and its younger sister, Hepatology, gradually acquired respect as an autonomous field early in the 1970s, with the formation of the Pediatric group for Gastroenterology, and more recently in 1992 with the creation of the Italian Society for Pediatric Gastroenterology and Hepatology in the Italian Society of Pediatrics. My aim in this paper is to review the most significant developments that have taken place in Pediatric Hepatology over the past decade, and to indicate how the field is likely to develop in the future. I will make particular reference here to HBV infection, cholelithiasis, extrahepatic biliary atresia, and liver transplants.

HBV Infection

In Italy, this remains one of the most common causes of chronic hepatitis in children. (HCV infection in children without an underlying illness is still uncommon). Since the 1960s, we have gained an understanding of the risk factors, pathogenesis and natural history of infection, and an awareness of the strong tendency for the condition to become chronic in children. Moreover, with the increase in knowledge of the biology of the virus, an efficacious programme of preventive medicine has been implemented, which 3 years ago culminated in obligatory vaccination for newborns and 12-year-old children. These measures have resulted in a change in the epidemiology of the infection, which is now found above all in foreign children residing in Italy, who have been usually adopted.

Over the last 10 years, the phenomenon of international adoption represents a new socio-sanitary reality in the industrialized countries. A number of important studies report that, more than 50 percent of foreign children adopted present serious medical condition (irrespective of the area of the world from which they come, be it Asia, Africa, South America, or Eastern Europe). If routine screening is not carried out, these disor-

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ders go undetected by medical tests performed in the children's countries of origin, as well as by medical examinations carried out in their adoptive countries [4]. The most frequent diseases are infections, and amongst these HBV infection, besides TBC and CMV infection, making those children in whom such infections go undetected veritable spring of disease [3].

Two clinical patterns of chronic HBV infection have been observed in foreign children which are different from those observed in Italian children. The first type is found in children whose clinical and nutritional state is most compromised, who present an important immunological response as soon as their sanitary environment and nutrition improve, with peaks of cytolosis and sometimes irreversible hystological damage occurring. Virus replication stops more quickly than in Italian children, and frequently also takes place with HBsAg clearance, an occurrence that is most unusual in Italian children.

The second pattern of HBV infection, more frequently seen in eutrophic children, is characterised by the high levels of viremia and little or no presentation of cytolosis, which typifies chronic asymptomatic carrier with normal transferases. This pattern contrasts with that we have learnt to recognise in the great majority of Italian children, where infection and disease coincide. These features result from an antigenic tolerance arising from early exposure to the virus which produces an unsatisfactory response to Interferon treatment.

The 1980s were a decade of experimentation with Interferon treatment. This proved more effective in European than in Asian children, presumably because the former are infected later than the latter. However, hopes of a radical solution to the problem have hitherto been thwarted: complete eradication of the virus is extremely rare, and the goal of Interferon treatment has instead become that of stopping its replication. Depending on the lenght of treatment and dosage, the success rate varies slightly, but the end of replication of the virus is achieved in only one in three patients on average, a slightly lower success rate than in adults. This is probably due to a high degree of viral replication in children. Although they may show no symptoms of the illness, once these chronic carriers of HBV reach adulthood, pediatricians merely consign them to adult doctor, aware of fact that the problem has not been entirely resolved. Monitoring of chronically infected patients such as these who contracted the virus in childhood should probably be of a different kind, with attention being paid to possible neoplastic development.

In conclusion, even if Interferon has certainly proved to be more effective than placebo treatment, in children as well as adults, the results are nonetheless unsatisfactory and should spur the development of improved therapies in the future. The goal which should now be pursued is clearly that of primary prevention of the infection. The greatest progress to date has been made in vaccination against HBV, to the extent that in another twenty years we will probably have defeated the virus.

Cholelithiasis

Cholelithiasis is a disease that has been increasingly reported in children in the past 10 years. It was previously believed not to occur in pediatric age, but its diagnosis in children has become quite common with the advent of ultrasound scanning [2, 8]. It can affect children of any age, from newborns to adolescents, and signs of the disease can

even be detected at the fetal stage (some 30 such cases have been reported in the literature, two of which have been in studies of ours). The true incidence of cholelithiasis is not known however, as there have been few epidemiological studies. One such study, conducted at the University of Bari on a group of children aged between 4 and 19 years of age, reports an incidence rate of the disease of 0.13%, approximately ten times lower than in young adults (as is well known, the incidence of cholelithiasis increases with age).

Unlike in adults, where females are more often affected, the disease occurs in children with equal frequency in males and females. In Italy, moreover, 3 out of 4 adults affected by cholelithiasis present cholesterol stones, while in children under 6 years, pigment stones are more frequent (as far as we know, in that very few studies of this subject have been undertaken). However, contrary to what was believed only a few years ago, it can be seen from selected series that hemolytic diseases secondary stones occur in a minority of patients (less than 1 in 3). The incidence of secondary stones in such patients increases with age. In the case of sickle cell anaemia, for example, stones occurred in 14% of patients under the age of 10, in 36% of those under the age of 20, and in more than 50% of patients aged over 20.

In children, then, the formation of pigment stones is caused by different factors from hemolysis, above all parenteral nutrition, which is widely used in neonatal intensive-care units. In such patients, the risk of cholelithiasis (reported as high as at 40% in some studies, and at 9% in our own) seems to be correlated to prematurity, to fasting, and to the duration of parenteral nutrition, as well as to diseases or surgical resection of the last ileal loop. Minimal enteral nutrition, which causes intermittent contractions of the gall bladder, reduces the risk of stones in these children. Chronic liver diseases, cholestasis, disorders of the biliary tree, Wilson's disease, and indeed cystic fibrosis of the pancreas all run a higher risk of pigment than cholesterol stones. This is due to the fact that contrary to what was previously believed, a reduction in the bile salt secretion is accompanied by a simultaneous decrease in cholesterol synthesis, with normal cholesterol bile salt ratio.

Besides the conditions described above, the use of certain drugs (Ceftriaxone and Furosemide) increases the risk of pigment stones, which have also been reported in the newborn infants of morphine addicts. Biliary infections also predispose patients to pigment stones. As has already been observed, cholesterol stones, seem to occur less frequently before puberty. Even if very little information is available on the composition of lipids and on cholesterol saturation in children's bile, there is some evidence to suggest that, with the exception of the neonatal period and puberty, the child's bile is relatively undersaturated with cholesterol, compared with adults.

In adults, obesity is recognized as a notable risk factor for cholesterol cholelithiasis, while little or anything is known of this risk in children. We made a hepatic ultrasound scan to 30 obese patients with signs of damage to the liver: steatosis was present in all patients, while none presented calculi. All the conditions which interrupt the enterohepatic circulation of the biliary acids – disease and or resection of the last ileal loop – are known to predispose adults to cholesterol cholelithiasis. In children, on the other hand, also in this condition, pigment stones are more frequently reported than cholesterol stones. This is due to the frequent association of pigment stones with conditions requiring parenteral nutrition or diuretics treatment in the neonatal period, and also due to the

fact that the few studies of pre-pubertal children with resection or pathology of the last ileal loop report an absence of cholesterol supersaturation in the bile. Hormonal influences play an undeniable role in the pathogenesis of cholesterol cholelithiasis; studies of two groups of female adolescents, aged between 14 and 20, both report a marked association between the presence of stones, parity and obesity, and a less noteworthy association between the presence of stones and the use of oestroprogestins.

Little is known about the natural history of cholelithiasis in infancy. In our experience, the majority of patients present no symptoms (70% of patients under six years). Generally, patients asymptomatic at diagnosis fail to present symptoms in subsequent periods of observation, confirming the impression that, as in adulthood, asymptomatic cholelithiasis is a benign condition. We observed calculus migration to the choledocus in only 2 out 60 such infants. In the first month of life, and subsequently, to a lesser extent, a spontaneous resolution of cholelithiasis can occur (in 4 out of 13 infants in our experience), which indicates a policy of non-intervention during the first year of life. An optimum treatment strategy has yet to be determined. Many of us in the field adopt an analogous strategy to that employed with adults, and do not treat asymptomatic cholelithiasis, except in those patients presenting hemolysis. However, children's long life expectancy makes such an approach at least questionable (the example of cholelithiasis detected at the fetal stage illustrates this point particularly aptly).

We treated 10 successive patients presenting radiotransparent calculi of less than 1 cm's diameter with UDCA therapy for a year. Although patients withstood the treatment well, and it was effective in treating their symptoms, in no patient did it alter the number and size of the calculi. The recent introduction of laparoscopic surgery in pediatric age may make surgical decision-making easier, also given the low probability of successful UDCA treatment. Therapeutic approaches to cholelithiasis must obviously be underpinned by a knowledge of pathogenetic mechanisms and of the natural history of the disease, however. This is a stimulating agenda for future work in the field.

Atresia of the Extrahepatic Bile Ducts

According to Kasai, hepato-porto enterostomy constitutes an important step forward of the last twenty years in the treatment of extrahepatic biliary atresia (EHBA). The operation, first conceived of in the 1950s, was introduced slowly into European and North American surgical practice. It has been carried out in Italy since the 1970s. Before then, at least 15% of patients with EHBA could be operated on, while for the rest biliary cirrhosis with complications, hepatic failure and premature death within the first two years of life was inevitable.

The appearance from the beginning that the outcome of the operation was directly related to early diagnosis makes it necessary to consider the operation a surgical semi-urgency. At first, the deadline for surgery was considered to be the first three months of life: however, even if in 2 out 3 cases the bile drainage was re-stabilized in the short term, disappearance of jaundice only occurred in 30% of cases. While 32% of patients survived to the age of 10, only half were anicteric and only 1 in 4 had normal hepatic tests. The advent of the liver transplant as a truly effective treatment immediately provoked controversy in the 1980s over the usefunlness of hepato-porto enterostomy as an

initial therapy for EHBA. What soon became clear was that it was the age at which patients were treated which was debateable rather than the surgery itself. Indeed, King's College Hospital of London [6] reported that 86% of infants operated on before 2 months presented normal bilirubin levels by the age of 1, and the Bicêtre team [1] reported that 80% of infants operated on before 45 days survive to present with normal bilirubin levels by the age of 3. In Kasai's group, 87% of patients jaundice free survived to the age of 15. If the risk of reoccurrence of jaundice (cholangitis is the most frequent and dangerous cause) can be excluded, it is to be hoped that these good initial results will mean that transplants can be avoided in the great majority of cases.

However, EHBA should be diagnosed as early as possible. Greater alertness to the warning signs is needed: these include a cystic image of the liver on antenatal ultrasound scans, persistently stools with no yellow pigment, and lastly, jaundice beyond 14 days. It is hoped that earlier surgery, before 45 days, will improve the final prognosis and in doing so reduce the number of patients needing a liver transplant.

In conclusion, if liver transplant is the last resort in the treatment of EHBA, the first step remains hepato-porto enterostomy however. If this is carried out early enough it can either permanently cure the disease or at least ensure infant's survival to an age at which a liver transplant can be carried out.

Liver Transplantation

Some of the most significant developments in medicine over the past ten years have taken place in this area. Indeed, the past, present and future are rapidly converging here as increasingly important results are obtained. Liver transplants have been carried out for 30 years, but only, since the National Institute of Health's Consensus Conference of 1983, it is considerate an efficacious surgery rather than an experimental procedure. Greater knowledge concerning the liver, increasingly sophisticated surgical techniques, the improvement of post-surgical care, the control of infection, and above all the improvement of immunosuppressive therapy have all undoubtedly contributed to this transformation. Results in children are even better than in adults: 70-80% of patients survive to the age of 5 [7].

A number of unresolved difficulties remain, however, and many of these are of a cultural and organizational nature. The technique of reduced and split liver transplantation is a response to the problem represented by a shortage of organs, future remedies for which might include living transplant xenograft and hepatocites transplant. It is estimated that some 500 adult transplants are needed in Italy each year. An approximate corresponding pediatric figure of 50 can be roughly estimated by extrapolation (considering the occurrence of those diseases which are most frequent indication for liver transplantation). In Italy, liver transplants in children have been carried out in Milan since 1987, and more recently, in Rome and Padua too. The quality of these operations is comparable to those performed in the most advanced nations.

Nonetheless, less than 50 children have been operated on to date in Italy, and it is my belief that we need to do our utmost to win confidence in liver transplant in Italy and ensure that our children receive what they need and are entitled to, above all at lower personal, but also lower social cost.

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